Methods Used to Conduct and Report Bayesian Mixed Treatment Comparisons Published in the Medical Literature: A Systematic Review

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Methods Used to Conduct and Report Bayesian Mixed Treatment Comparisons Published in the Medical Literature: A Systematic Review

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ABSTRACT

Objectives: To identify published Bayesian mixed treatment comparisons (MTCs) and to summarize characteristics regarding their conduction and reporting.

Design: Systematic review.

Methods: We searched multiple bibliographic databases (January 2006-July 31, 2011) for full-text, English language publications of Bayesian MTCs comparing the effectiveness or safety of ≥3 interventions based on randomized controlled trials and having at least one closed loop. Methodological and reporting characteristics of MTCs were extracted in duplicate and summarized descriptively.

Results: We identified 34 Bayesian MTCs spanning 13 clinical areas. Publication of MTCs increased over the 5-year period; with 76.5% published during or after 2009. MTCs included a mean (± standard deviation) of 35.9±30.1 trials (n=33,459±71,233 subjects) and 8.5±4.3 interventions (85.7 % pharmacologic). Non-informative and informative prior distributions were reported to be used in 44.1% and 8.8% of MTCs; respectively, with the remainder failing to specify the prior used. A random-effects model was used to analyze the networks of trials in 58.5% of MTCs, all using WinBUGS; however, code was infrequently provided (20.6%). More than two-thirds of MTCs (76.5%) also conducted traditional meta-analysis. Methods used to evaluate of convergence, heterogeneity and inconsistency were infrequently reported, but from those providing detail, methods appeared varied. MTCs most often used a binary effect measure (85.3%) and ranking of interventions based upon probability was common (61.8%), although rarely done pictorially (8.8% of MTCs). MTCs were published in 26 different journals with a mean impact factor of 9.51±8.75. While 73.1% of journals imposed limits on word counts and 50% limits on the number of tables/figures, online supplements/appendices were allowed in 80.8% of journals.

Conclusion: Publication of Bayesian MTCs is increasing in frequency, but details regarding their methodology are often poorly described. Efforts in clarifying the appropriate methods and reporting of Bayesian MTCs should be of priority to thought leaders.

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Article Summary

Article focus

- To identify published Bayesian mixed treatment comparisons (MTCs) and to summarize characteristics regarding their conduction and reporting.

Key messages

- We identified 34 Bayesian MTCs spanning 13 clinical areas, published in 26 different journals.
- Publication of Bayesian MTCs is increasing in frequency, but details regarding their methodology are often poorly described. Efforts in clarifying the appropriate methods and reporting of Bayesian MTCs should be of priority to thought leaders.

Strengths and limitations of this study

- Our systematic review adds to this existing literature by updating results and adding new information as prior reviews only included literature through 2007/2008. Unlike prior publications, our systematic review focused only on Bayesian MTCs of networks with at least one closed loop.
- Unlike prior review, we evaluated additional model characteristics in depth including testing for model fit, evaluation of convergence, adjustment for covariates or multi-arm trials, the specific priors used and availability of the code and aggregated study-level data.
- An important limitation of our review is that we cannot say with certainty that a lack of reporting means a given method or analysis was not undertaken (i.e., the testing for convergence or inconsistency need not be described in a paper for it to have been performed by the investigators) or that the reporting of a piece of data or statistical code was not considered.

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Competing Interests:

The authors of this publication have no competing interests to declare.

Data Sharing:

Individual study data that has been extracted can be found by accessing the full report on the AHRQ EHC website.

Study Approval/Ethics:

This study did not include human subjects therefore ethics/institutional review board approval was not obtained.

INTRODUCTION

Clinicians and decision makers often have to select from multiple available interventions when determining the optimal treatment for a disease. Ideally, high-quality randomized controlled trials (RCTs) that estimate the effectiveness of all possible interventions directly against one another would be available to guide decision-making.[1-4] However, interventions are commonly compared with placebo or non-active control in RCTs rather than another active intervention, and when direct comparative trials exist they are between only two intervention from a larger group of possible treatments. As such decision-makers are faced with a lack of adequate direct comparative data to make their judgments.

In the absence of direct comparative data, indirect comparisons may provide valuable information. For example, if two different interventions have been evaluated against a common comparator, the comparative effects of the two interventions compared with each other can be estimated indirectly.[1, 2] Even in the presence of direct comparative data, indirect comparisons may add value to the interpretation of comparative effectiveness by improving precision of treatment effect estimates.

Several methodologies exist to indirectly compare interventions, as do modes to implement such methodologies.[1, 5-8] In the simplest form, interventions that are evaluated against a common comparator in separate trials can be compared to each other indirectly using an anchored indirect treatment comparison approach.[5] As a generalization of indirect comparisons, when more than two treatments are being compared indirectly, and at least one pair of treatments is being compared both directly and indirectly (a closed loop is present), both direct and indirect types of data can be used to estimate effects in a MTC meta-analysis using a Bayesian or frequentist framework.[1-8] Prior research has attempted to categorize the use of indirect comparisons in the medical literature, but either did not included Bayesian MTCs or collected limited data on this approach.[9-10] The Agency for Healthcare

Research and Quality commissioned us to evaluate how MTCs in published systematic reviews are conducted and reported. Here, we present the findings of our systematic review from this report identifying MTCs using a Bayesian framework and descriptively summarize their methodological and reporting characteristics.

METHODS

A systematic literature search was conducted in MEDLINE, the Centre for Reviews and Dissemination Databases (including the Database of Abstracts and Reviews of Effects, Health Technology Assessment and the National Institute for Health Research Economic Evaluation Database), The Cochrane Library, and the American College of Physicians Journal Club from January 1, 2006 through July 31, 2011. The search strategy in **Appendix 1** was used.

Two independent investigators assessed citations for inclusion in a parallel manner based on *a priori* defined criteria. Specifically, we included meta-analyses that compared the clinical effectiveness or safety of interventions [any pharmacologic (including placebo and different doses), behavioral or procedural interventions] based on RCTs, utilized a Bayesian approach to conduct MTC and were published in full-text and in the English language. There has been inconsistency in what constitutes a MTC in the medical literature;[11] therefore, for the purposes of this systematic review a MTC was defined as the comparison of three or more interventions and a network pattern that contained at least one closed loop (**Appendix 2**). Methodological publications that presented MTCs for illustrative purposes and cost-effectiveness analyses were not considered in this systematic review, nor were individual patient data meta-analyses.

Two reviewers independently extracted data with disagreements resolved through discussion. For each included Bayesian MTC, all published material including the manuscript, supplements, appendices or external websites which the reader of the article was referred to for additional information were used during data extraction. Therefore, the extraction of data was predicated on the reporting of the information by the authors within these sources. When extracting data, we recorded what the authors reported without ourselves judging whether the methods were appropriate or not. If there was insufficient data from all available sources, we indicated "not reported" for that criterion on data extraction.

General characteristics of each MTC were extracted including author and funding information, if a methodologist was an author, the number and type of intervention comparisons made, number of printed pages and use of supplement or appendix, the number of trials and patients in the analyses, clinical area (e.g., cardiology, endocrinology) and the network pattern. For the purpose of this project, we defined a methodologist as an individual having an affiliation with a department of statistics, biostatistics, epidemiology, clinical epidemiology or public health services, as determined by author information and affiliations listed in the publication.[13] The country in which a review was conducted was determined by the corresponding author's affiliation.

The network pattern [3, 4, 13, 14] was determined by figures presented within the identified publication. If a figure was not available, we as investigators determined the pattern based on text descriptions of included trials.

We also extracted information regarding the methodology used to conduct the Bayesian MTC including the models applied (e.g., fixed vs. random effects), description of model parameters (e.g., choices of prior distributions), methods for assessment of model fit, potential bias, inconsistency and heterogeneity, use of covariate adjustment in models, whether the model accommodated multi-arm trials, software utilized, and availability of code.

Finally we extracted data concerning the reporting of results including the type of endpoint (e.g., binary vs. continuous), effect size and measure of variance, use of other methods to report results (e.g., probability of treatment being best, claims of equivalence or non-inferiority); and the format/presentation of results (e.g., text, tables, figures). Characteristics of the journals in which included MTCs were published were collected, including journal name, impact factor, allowance of supplements or appendices, and limitations on word, table and figure counts.

The characteristics of the Bayesian MTCs and journals were summarized descriptively. Categorical data is presented using frequencies and continuous data as means ±standard deviations (SDs).

RESULTS

A total of 626 citations were identified through the database searches with an additional five MTCs identified through manual review (**Figure 1**). After full text review, 35 articles representing 34 unique Bayesian MTCs were included.[15-49] The publication by Orme and colleagues[25] analyzed two distinct networks of RCTs.

The rate of publication of Bayesian MTCs increased over the 5-year search period, with 26 (76.5%) of the MTCs published between 2009 and2011 compared to only 8 published prior to 2009. On average, 6.1±4.8 authors were listed per publication and less than half of publications (47.1%) included a methodologist as an author (**Table 1**). The most common country from which authors published MTCs was the United Kingdom (35.3%), followed by the United States (11.8%) and Greece (11.8%). The remaining analyses were published by authors based in a variety of countries.

Funding sources for the MTCs included governmental/foundation (29.4%), industry (26.5%) and unfunded (17.6%), with23.6% not making a statement regarding funding source(s). Only two analyses identified an organizational affiliation, one each with the Health Technology Assessment Program and The Cochrane Collaboration. The mean number of printed pages per MTC publication was 16.6±36.3 (range 4 to 221) and over half published a supplement or appendix. Only one publication from those that did not publish a supplement or appendix did not have the option to do so given journal (or report) specifications.

There were 13 different categories of disease states evaluated in identified Bayesian MTCs. The mean number of interventions included within the analyses was 8.5±4.3, of which most were pharmacologic (85.7%) in nature. The mean number of trials included in the MTCs was 35.9±30.1 and the mean number of patients included was 33,459±71,233 (range 594 to 324,168).

The most common model used in Bayesian MTCs was a random-effects model (58.5%) (**Table 2**). Very few analyses reported information about whether there was adjustment for covariates (25.6%). Of the 28 MTCs that included trials with three or more arms, 10 (35.7%) analyses reported use of an adjustment for multi-arm trials. Less than half of the analyses reported testing the model fit. Of the 15 analyses that reported testing model fit in some manner, the most common method was use of residual deviance (40.0%). More than two-thirds of the Bayesian MTCs (76.5%) also included a traditional meta-analysis.

All MTCs used WinBUGS software, and two also specified the use of additional software including the BUGS XLA Wrapper and S-Plus. The statistical WinBUGS code was made available to the reader in only 20.6% of cases and, of these, it was most often found in an online supplement/appendix (71.4%). Aggregated study-level patient data used in the MTC was frequently made available to the reader, and of the 21 analyses (61.8%) that published such data, it was most commonly found in the manuscript itself (85.7%). Evaluation of convergence was found in 35.3% of analyses and, of these, the most common method was the Gelman-Rubin statistic (58.3%), although several less frequent methods were used as well.

Utilized priors were reported as either non-informative (vague or flat) or informative in 44.1% and 8.8% of analyses, respectively. The remaining analyses (47.1%) did not specify the nature of the prior distributions used. It was also uncommon for the actual prior distribution to be reported for the population treatment effect (d) and the between-study standard deviation of population treatment differences across studies (sigma); with only 32.4% and 29.4% of MTCs, respectively, reporting this information. Sensitivity analyses based upon priors were conducted in 11.8% of MTCs.

Evaluation of heterogeneity within accompanying traditional meta-analyses was common (61.5%). The most common method used to assess heterogeneity was the I^2 statistic (81.3%) followed by the Cochrane Q-statistic (43.8%), among many less frequent methods. Evaluation of heterogeneity within the MTC was less common, reported in only 32.4% of publications. Of these 11 analyses, tau^2 (among-study variance of true effects) was used in 54.5% of analyses followed by between-study standard deviation (45.5%) and several other less frequent methods (some MTCs reported multiple means to test for heterogeneity and therefore are counted twice in the numerator).

Inconsistency between indirect and direct estimates was evaluated in 24 (70.6%) studies. One review reported being unable to evaluate inconsistency due to lack of direct data while the remaining MTCs simply did not comment on inconsistency. The most common method used to evaluate inconsistency was comparing results of the MTC to those of with either a traditional meta-analysis conducted by the authors simultaneously or a previously published traditional meta-analysis.

Most analyses (85.3%) reported outcomes that were binary **(Table 3)**. Of these 29 analyses, odds ratios were the most commonly reported effect measure (62.1%), followed by relative risks (17.2%) and hazard ratios (13.8%), among other less frequent measures. Of the 10 (29.4%) analyses that reported continuous outcomes, the weighted-mean difference was the most common effect measure (80.0%). All analyses reported variance with 95 percent credible intervals and one also reported standard errors. Most analyses did not report if the posterior distribution was the mean or median value (85.3%). Presentation of results data varied, although most analyses used multiple media including tables, figures, and text.

Few analyses (8.8%) presented graphical representations of the posterior distributions of outcomes. Rank-ordering of interventions based on probability statements (including rankograms with the probability of a treatment being best, second best, and so on) for a given outcome was reported in 21 (61.8%) of the MTCs. Only one MTC made claims of equivalence and two made claims of non-inferiority, and of these, two defined the minimally important difference required to make this determination.

Complete details of each journal in which at least one MTC was published can be found in **Tables 4 and 5**. The 34 MTCs were published in 26 different journals, with a mean impact factor of 9.51±8.75. The British Medical Journal published the most Bayesian MTCs (5 of the 34, 14.7%) followed by Current Medical Research and Opinion (4 of the 34, 11.8%). The majority of journals (73.1%) imposed word count limits and 50% imposed table/figure limitations; however, 80.8% of journals allowed online supplements or appendices.

DISCUSSION

Meta-analysis has been regarded as the most highly cited study design in health science.[50] However, a drawback of the traditional meta-analysis is its ability to compare only two interventions, without the ability to simultaneously evaluate other comparators. This is inconsistent with clinical practice as in many instances there are a variety of interventions that exist and one must decide which is best. The use of statistical methods (including simple approaches as well as MTC meta-analysis) to compare greater than two interventions simultaneously is on the rise within the peer-reviewed literature. As recent as 2005, a search of the medical literature yielded four publications that utilized such methods; while in 2011, the number increased to 57.[11] The results of our systematic review also suggest that indirect comparisons, specifically Bayesian MTC, have become more prevalent. Moreover, identified Bayesian MTCs were published in a wide variety of journals covering a range of disease states and thus likely to reach a large readership given their collective mean impact factor.

Bayesian MTCs are often criticized for requiring the use of prior information (which is most commonly non-informative) and its need to be run with non-user friendly software.[14] Despite this fact, a recently published survey of Cochrane systematic review authors found that most accept indirect evidence as a source of data comparing relative effectiveness of interventions.[51] Although many of the authors had some knowledge of indirect comparison methods, the majority reported never having used such methods and felt they needed more training in this field. To date, there seems to be only limited guidance as to how to conduct and report a MTC,[14] creating an environment of inconsistency in the literature.

Prior research by Donegan and colleagues has attempted to categorize published indirect comparisons and evaluate their quality, although advanced methods including Bayesian (and frequentist) MTCs were not included.[9] Of the 43 included comparisons, 23 used an anchored indirect approach while others used hypothesis testing, confidence interval overlap, and meta-regression methods to draw indirect comparisons. The authors concluded that quality of published indirect comparisons, in particular the assessment of model assumptions and the methods used to do so, were suboptimal. A set of quality criteria were proposed by the authors to be used in future indirect comparisons, specifically evaluating if the method of indirect comparison applied was appropriate, if methods to assess similarity, homogeneity and consistency were stated and if such methods were appropriate, and details of overall interpretation and reporting of results.

Song and colleagues also have systematically reviewed previously published indirect comparisons and, of the 88 identified, found only 18 using "network or Bayesian approaches".[10] Their findings are similar to that of Donegan and colleagues, suggesting that the main methodological problems included unclear understanding of assumptions, incomplete inclusion of relevant studies, flawed or inappropriate methods, lack of similarity assessment and inappropriate combination of direct and indirect evidence.

Our systematic review adds to this existing literature by updating results and adding new information. First, the abovementioned prior reviews only included literature through 2007/2008, making ours the most up-to-date review available. Unlike prior publications, our systematic review focused only on Bayesian MTCs of networks with at least one closed loop, perhaps the most common method utilized of late to analyze complex networks of RCTs. While prior publications focused on the evaluation and reporting of assumptions made within the models, we evaluated additional model characteristics in depth including testing for model fit, evaluation of convergence, adjustment for covariates or multi-arm trials, the specific priors used and availability of the code and aggregated study-level data. Despite these differences however, our findings are consistent with prior research and with the opinion of experts regarding the challenges and concerns around implementing and reporting these more complex statistical methods.[10, 11, 52] Perhaps more clear guidance as to how to conduct and report these types of meta-analyses will lead to a more optimal and consistent approach.

While we only characterized the methods and reporting of Bayesian MTC in this report, our search strategy was designed to capture MTCs regardless of methodological approach (including frequentist MTC). Of note, only a handful (n=9) of frequentist MTCs were identified in our search, three of which specifically reference using the methods for MTC proposed by Lumley and colleagues, while the others more generically referenced mixed-model approaches.[49, 53-60] This suggests that meta-analysts at present seem to favor a Bayesian approach to MTC, since investigators could have chosen to use either a Bayesian or Frequentist method for any of the MTC identified in our search (given all analyzed networks with at least one closed loop). Given the relative paucity of frequentist models, we do not describe the characteristics of their methods and reporting in this paper but they can be found elsewhere [14].

An important limitation of our review is that we cannot say with certainty that a lack of reporting means a given method or analysis was not undertaken (i.e., the testing for convergence or inconsistency need not be described in a paper for it to have been performed by the investigators) or that the reporting of a piece of data or statistical code was not considered. However, we evaluated word, table and figure limits imposed by journals in which these MTCs were published and our findings do not suggest journal space should be an obstacle to complete reporting.

With the growing publication of Bayesian MTCs in the peer-reviewed literature and the recognized challenges of such methods, the appropriate use of this methodology and interpretation of such work becomes imperative. Efforts in clarifying the appropriate use and reporting of Bayesian MTC should be of priority to thought leaders.

Author contributions:

DMS, JCC, CIC, WLB, OJP and CMW were responsible for study design. DMS, WLB, and OJP were responsible for data collection. DMS, CIC, JCC were responsible for data analysis and interpretation. All authors contributed to drafting the manuscript and approved the final manuscript. CIC is responsible for the overall content as the corresponding author.

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Competing Interests

None

Data Sharing

Individual study data that has been extracted can be found by accessing the full report on the AHRQ EHC website.

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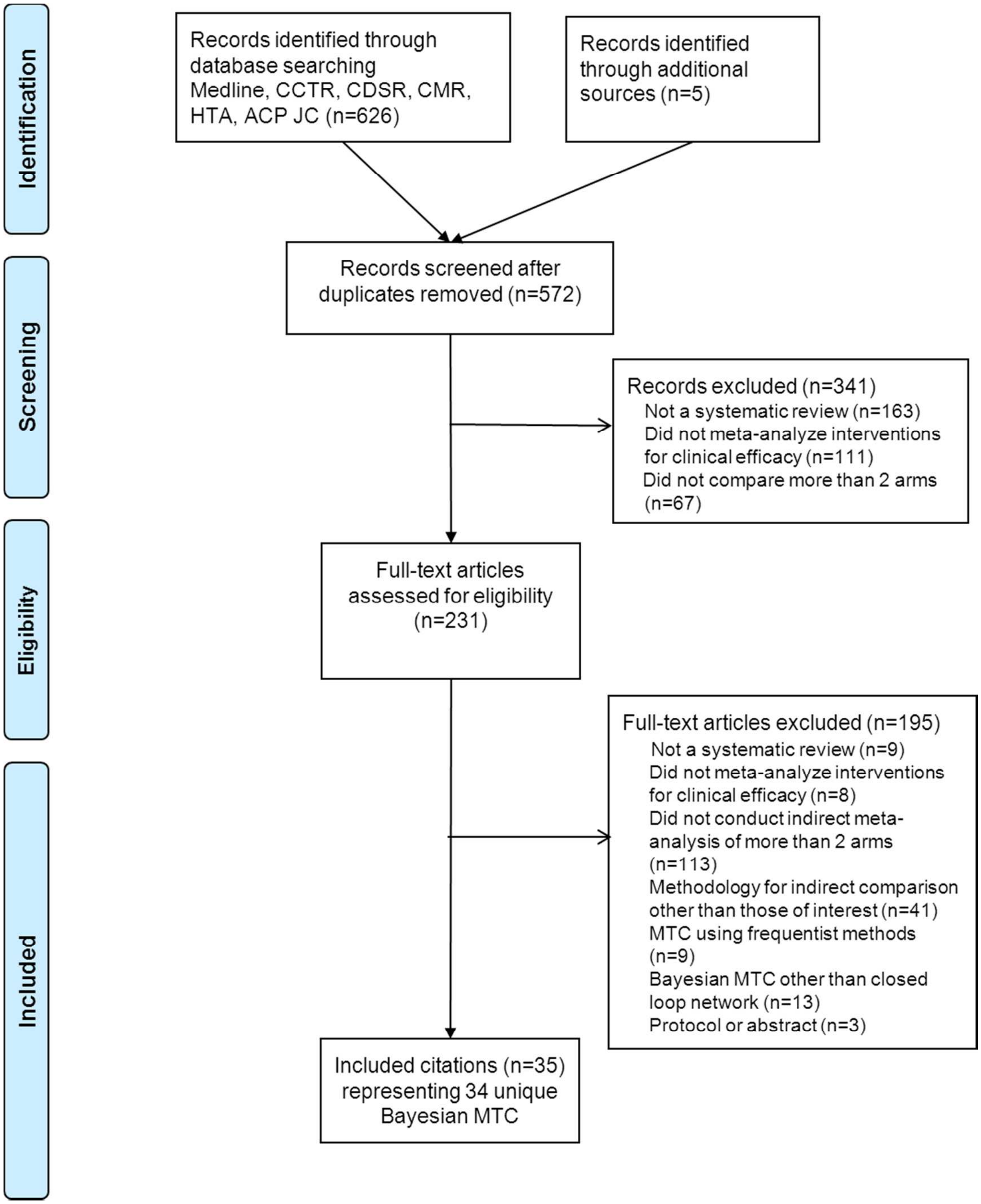
Figure 1. Flow diagram of citation inclusion and exclusion



Abbreviations: ACP JC= American College of Physicians Journal Club; CCTR=Cochrane Central Register of Controlled Trials; CDSR=Cochrane Database of Systematic Reviews; CMR=Cochrane Methodology Register; HTA=Health technology Assessment; MTC=mixed treatment comparison

Table 1. General characteristics of Bayesian mixed treatment comparisons

Characteristic	n/N (%) or Mean (SD)
Number of authors	6.1 (4.8)
Was a methodologist an author on the manuscript?	16/34 (47.1)
Country	
U.S.A.	4/34 (11.8)
United Kingdom	12/34 (35.3)
Canada	2/34 (5.9)
Brazil	1/34 (2.9)
China	2/34 (5.9)
Switzerland	3/34 (8.8)
Netherlands	1/34 (2.9)
Italy	3/34 (8.8)
Belgium	1/34 (2.9)
Greece	4/34 (11.8)
Funding	
Industry	9/34 (26.5)
Government/Foundation	10/34 (29.4)
Unfunded	6/34 (17.6)
Other	1/34 (2.9)
Not reported	8/34 (23.6)
Declared affiliation	2/34 (5.9)
Health Technology Assessment Program	1/2 (50.0)

The Cochrane Collaboration	1/2 (50.0)
Number of printed pages	16.6 (36.3)
Supplement or appendix published	20/34 (58.8)
Disease state evaluated	
Behavioral health	4/34 (11.8)
Cardiology	6/34 (17.6)
Infectious disease	2/34 (5.9)
Endocrine	2/34 (5.9)
Pulmonary	2/34 (5.9)
Pain	3/34 (8.8)
Dermatology	2/34 (5.9)
Ophthalmology	2/34 (5.9)
Rheumatology	2/34 (5.9)
Gastroenterology	3/34 (8.8)
Dental	1/34 (2.9)
Oncology	4/34 (11.8)
Substance abuse	1/34 (2.9)
Number of interventions compared*	8.5 (4.3)
Type of intervention*	
Pharmacologic	30/35 (85.7)
Devices	3/35 (8.6)
Other	1/35 (2.9)
Device and pharmacologic	1/35 (2.9)

Number of trials included in network*	35.9 (30.1)
Number of patients included in network*	33,459 (71,233)

*The trial by Orme et al. included two individual networks and they are considered separately for this characteristic

Table 2. Methods characteristics in Bayesian mixed treatment comparisons

Characteristic	n/N (%)
Conducted traditional meta-analysis	26/34 (76.5)
Model	
Fixed effects	1/34 (2.9)
Random effects	20/34 (58.8)
Fixed and random effects	7/34 (20.6)
Not reported	6/34 (17.6)
Adjustment for covariates	9/34 (25.6)
Adjustment for multiple arms in MTCs including trials with three or more arms	10/28 (35.7)
Model fit tested	15/34 (44.1)
Residual deviance	6/15 (40.0)
Deviance information criterion	2/15 (13.3)
Residual deviance and deviance information criterion	3/15 (20.0)
Q-Q plots	1/15 (6.7)
Mean sum deviation	1/15 (6.7)
Method not reported	2/15 (13.3)
Code published	7/34 (20.6)
Online supplement	5/7 (71.4)
External website	2/7 (28.6)
Aggregate study-level data published	21/34 (61.8)
Manuscript	18/21 (85.7)

Online supplement	2/21 (9.5)
External website	1/21 (4.8)
Evaluation of convergence*	12/34 (35.3)
Gelman Rubin statistic	7/12 (58.3)
Kernel density plot	1/12(8.3)
Visual plot inspection	1/12 (8.3)
Observation of chain mix	2/12 (16.7)
Method not reported	2/12(16.7)
Priors	
Use of noninformative	15/34 (44.1)
Use of informative priors	3/34(8.8)
Not specified	16/34 (47.1)
Prior distribution of d reported	11/34 (32.4)
Prior distribution for sigma reported	10/34(29.4)
Sensitivity analysis based on priors	4/34 (11.8)
Evaluation of heterogeneity in traditional meta-analysis*	16/26(61.5)
I^2	13/16 (81.3)
Cochrane-Q statistic	7/16 (43.8)
PICO statement	1/16(6.3)
Plot visualization	2/16 (12.5)
L'Abbe plot	1/16 (6.3)
Evaluation of heterogeneity in network meta-analysis*	11/34(32.4)
Precision (tau^2)	6/11 (54.5)

Between study SD	5/11(45.5)
Heterogeneity p-values	1/11 (9.1)
Evaluation of inconsistency*	24/34 (70.6)
Comparison to traditional or prior meta-analysis†	12/24 (50.0)
Inconsistency/incoherence factors	4/12 (33.3)
Posterior mean residual deviance	3/12 (25.0)
Method not reported	4/12 (33.3)
Trial sequential analysis	1/12 (8.3)
Overall inconsistency (σ^2w)	1/12 (8.3)

*Studies that used multiple methods to test heterogeneity were counted multiple times, in the respective categories

†Authors either compared results of the MTC to a traditional meta-analysis that they conducted concurrently or to a traditional meta-analysis that was previously published

Abbreviations: MTC=mixed treatment comparison; PICO=patient, intervention, comparator, outcome; SD=standard deviation

Table 3. Outcomes and results reporting in Bayesian mixed treatment comparisons

Characteristic	n/N (%) or Mean (SD)
Graphical representation of posterior distribution	3/34 (8.8)
Ranking of outcomes	21/34 (61.8)
Claims of equivalence	1/34 (2.9)
Claims of non-inferiority	2/34 (5.9)
Minimally important difference	8/47 (17.0)
Type of outcome	
Binary	23/34 (67.6)
Continuous	4/34 (11.8)
Binary and continuous	6/34 (17.6)
Categorical non-binary	1/34 (2.9)
Binary effect measure	29/34 (85.3)
Relative risk	5/29 (17.2)
Odds ratio	18/29 (62.1)
Hazard ratio	4/29 (13.8)
Multiple effect measures	2/39 (6.9)
Continuous effect measure	10/34 (29.4)
Weighted mean difference	8/10 (80.0)
Multiple	2/10 (20.0)
Categorical non-binary effect measure	1/34 (2.9)
Relative risk	1/1 (100)
Presentation of Results*	

Table	24/34 (70.6)
Text	32/34 (94.1)
Figure	21/34 (61.8
Posterior distribution	
Mean	1/34 (2.9)
Median	4/34 (11.8)
Not reported	29/34 (85.3)

*Studies were counted multiple times when more than one method was used.

Table 4. Aggregate journal characteristics

Characteristics	**Yes n/N (%) or Mean (SD)**
Impact factor	9.51 (8.75)
Supplement or appendix allowed	21/26 (80.8)
Online	19/21 (90.5)
Not specified	2/21 (9.5)
Word count limit	19/26 (73.1)
Table count limit	13/26 (50.0)
Figure count limit	13/26 (50.0)

Table 5. Individual journal characteristics

Journal	Included studies	Impact factor*	Supplement or appendix; format	Word count limit	Table limit	Figure limit
Alimentary Pharmacology & Therapeutics	Edwards, 2009a	3.861	Y, online	N	N	N
Annals of Internal Medicine	Gross, 2011	16.792	Y, not specified	3,500-4,000	4 tables or figures	4 tables or figures
Archives of Internal Medicine	Sciarretta, 2011; Cooper, 2006	10.639	Y, online	3,500	6 to 8 tables or figures	6 to 8 tables or figures
British Medical Journal	Baldwin, 2011; Hartling, 2011; Trelle, 2011; Wandel, 2010; Lam, 2007	13.471	Y, online	N	N	N
British Journal of Anaesthesia	Maund, 2011†	4.224	Y, online	5,000	N	N

Journal	Included studies	Impact factor*	Supplement or appendix; format	Word count limit	Table limit	Figure limit
British Journal of Cancer	Coon, 2009	4.831	Y, online	5,000-5,500	1 table reduces word limit by 200	1 figure reduces word limit by 200
British Journal of Ophthalmology	Van den Bruel, 2011	2.934	Y, online	3,000	5 tables or figures	5 tables or figures
Cancer Treatment Reviews	Golfinopoulus, 2009	6.811	N	N	N	N
Clinical Therapeutics	Edwards, 2009b	2.551	Y, online	5,500-6,000	N	N
Cochrane Database of Systematic Reviews	Walsh, 2010	6.186	N	N	N	N
Current Medical Research and Opinion	van de Kerkhof, 2011; Orme, 2010; Uthman, 2010; Vissers, 2010	2.609*	Y, online	11,200	N	N

Journal	Included studies	Impact factor*	Supplement or appendix; format	Word count limit	Table limit	Figure limit
Dermatology	Bansback, 2009	2.714	Y, not specified	13 pages for text, tables, figures	Included in page count	Included in page count
Drug and Alcohol Dependence	Meader, 2009	3.365	Y, online	6,000	N	N
Gastroenterology	Woo, 2010	12.023	Y, online	6,000	Minimum of 4 to 6 figures or illustrations	Minimum of 4 to 6 figures or illustrations
Health technology assessment (Winchester, England)	Maund, 2011†	4.197	N	N	N	N
The Journal of the American Medical Association	Phung, 2010	30	Y, online	3,500	4 tables or figures	4 tables or figures

Journal	Included studies	Impact factor*	Supplement or appendix; format	Word count limit	Table limit	Figure limit
Journal of Hospital Infection	Wang, 2010	3.078	N	5,000	N	N
Journal of Hypertension	Coleman, 2008	3.98	Y, online	N	N	N
Journal of the National Cancer Institute	Mauri, 2008; Kyrgiou, 2006	14.697	Y, online	6,000	8 table or figures	8 tables or figures
Lancet	Cipriani, 2009l Stettler, 2007	33.633	Y, online	4,500	"Should include about 5 illustrations"	"Should include about 5 illustrations"
Lancet Infectious Disease	Manzoli, 2009	16.144	Y, online	3,000-5,000	"Should include about 5 illustrations"	"Should include about 5 illustrations"
Lancet Neurology	Bangalore, 2011	21.659	Y, online	3,000-4,500	"Should include about 5 illustrations"	"Should include about 5 illustrations"

Journal	Included studies	Impact factor*	Supplement or appendix; format	Word count limit	Table limit	Figure limit
Lancet Oncology	Golfinopoulos, 2007	17.764	Y, online	3,000-5,000	"Should include about 5-6 illustrations"	"Should include about 5-6 illustrations"
Pharmacotherapy	Baker, 2009	2.631	N	7,000	N	N
Rheumatology	Nixon, 2007	4.171	Y, online	3,500	6 figures or tables	6 figures or tables
Value in Health	Dakin, 2010	2.342	Y, online	N	N	N

Abbreviations: Y: yes; N: no

*: The impact factor was obtained from Web of Science in 2012, except when the symbol appears for that journal the impact factor was not available in Web of Science and was taken from the journal's website.

†: Published as a manuscript and health technology assessment report, but counted as one unique publication

Appendix 1. Literature search

1. Randomized Controlled Trial/
2. Clinical Trial/
3. randomi$ control$ trial$.tw.
4. controlled clinical trial.sh.
5. clinical trial$.tw.
6. trial$.tw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. review literature/
9. meta-analysis.sh.
10. meta-analy$.tw.
11. metaanaly$.tw.
12. (meta adj analy$).tw.
13. 8 or 9 or 10 or 11 or 12
14. (indirect adj2 comparison$).tw.
15. (indirect adj2 evaluat$).tw.
16. (indirectly adj2 compare$).tw.
17. bayesian.tw.
18. (mixed treatment adj compar$).tw.
19. MTC.tw.
20. 14 or 15 or 16 or 17 or 18 or 19
21. 7 and 13
22. 20 and 21
23. limit 22 to english language
24. limit 23 to yr="2006 -Current"
25. remove duplicates from 24

Appendix 2. Network patterns

Examples of Networks with at least One Closed Loop

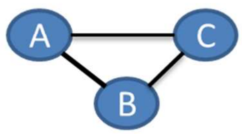


Figure 1

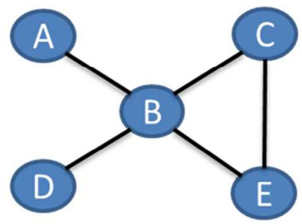


Figure 2

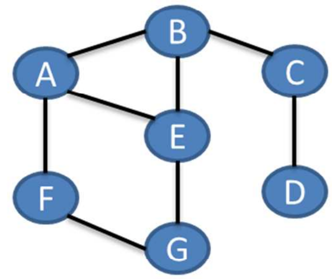


Figure 3

Examples of Networks without at least One Closed Loop

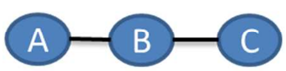


Figure 4

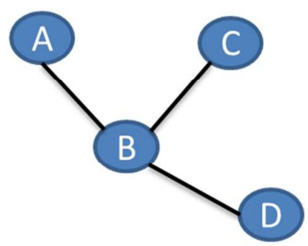


Figure 5

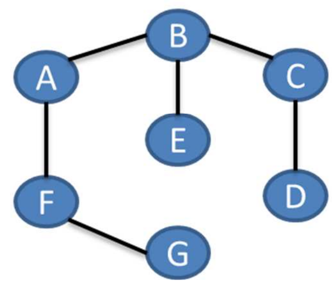


Figure 6

Here we provide examples of networks with (Figures 1-3) and without (Figures 4-6) at least one closed loop. A closed loop is defined as a comparison with a direct and indirect connection of evidence within the network. For example, in Figure 2, intervention B is compared to intervention C directly, but also indirectly through intervention E, making a closed loop. Presence of at least one closed loop defines the network as a mixed-treatment comparison.

Methods Used to Conduct and Report Bayesian Mixed Treatment Comparisons Published in the Medical Literature: A Systematic Review

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Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	Medical publishing and peer review
Keywords:	STATISTICS & RESEARCH METHODS, mixed treatment comparison, network meta-analysis

SCHOLARONE™ Manuscripts

Methods Used to Conduct and Report Closed Loop Bayesian Mixed Treatment Comparisons Published in the Medical Literature: A Systematic Review

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Keywords: mixed treatment comparison, network meta-analysis

Running title: Closed-loop Bayesian MTC methods and reporting

Word count: 2886

Tables: 5

Figures: 1

Appendices: 2

ABSTRACT

Objectives: To identify published closed-loop Bayesian mixed treatment comparisons (MTCs) and to summarize characteristics regarding their conduct and reporting.

Design: Systematic review.

Methods: We searched multiple bibliographic databases (January 2006-July 31, 2011) for full-text, English language publications of Bayesian MTCs comparing the effectiveness or safety of ≥3 interventions based on randomized controlled trials and having at least one closed loop. Methodological and reporting characteristics of MTCs were extracted in duplicate and summarized - descriptively.

Results: We identified 34 Bayesian MTCs spanning 13 clinical areas. Publication of MTCs increased over the 5-year period; with 76.5% published during or after 2009. MTCs included a mean (± standard deviation) of 35.9±30.1 trials (n=33,459±71,233 subjects) and 8.5±4.3 interventions (85.7 % pharmacologic). Non-informative and informative prior distributions were reported to be used in 44.1% and 8.8% of MTCs; respectively, with the remainder failing to specify the prior used. A random-effects model was used to analyze the networks of trials in 58.5% of MTCs, all using WinBUGS; however, code was infrequently provided (20.6%). More than two-thirds of MTCs (76.5%) also conducted traditional meta-analysis. Methods used to evaluate convergence, heterogeneity and inconsistency were infrequently reported, but from those providing detail, methods appeared varied. MTCs most often used a binary effect measure (85.3%) and ranking of interventions based upon probability was common (61.8%), although rarely displayed in a figure (8.8% of MTCs). MTCs were published in 26 different journals with a mean impact factor of 9.51±8.75. While 73.1% of journals imposed limits on word counts and 50% limits on the number of tables/figures, online supplements/appendices were allowed in 80.8% of journals.

Publication of closed-loop Bayesian MTCs is increasing in frequency, but details regarding their methodology are often poorly described. Efforts in clarifying the appropriate methods and reporting of Bayesian MTCs should be of priority.

Word count: 294 of 300

Article Summary

Article focus

- To identify published closed-loop Bayesian mixed treatment comparisons (MTCs) and to summarize characteristics regarding their conduct and reporting.

Key messages

- We identified 34 closed-loop Bayesian MTCs spanning 13 clinical areas, published in 26 different journals.
- closed-loop Bayesian MTCs is increasing in frequency, but details regarding their methodology are often poorly described. Efforts in clarifying the appropriate methods and reporting of Bayesian MTCs should be of priority.

Strengths and limitations of this study

- Our systematic review adds to this existing literature by updating results and adding new information as prior reviews only included literature through 2007/2008. Unlike prior publications, our systematic review focused only on Bayesian MTCs of networks with at least one closed loop.
- Unlike prior reviews, we evaluated reporting of additional model characteristics in depth including testing for model fit, evaluation of convergence, adjustment for covariates or multi-arm trials, the specific priors used and availability of the code and aggregated study-level data.
- An important limitation of our review is that we cannot say with certainty that a lack of reporting means a given method or analysis was not undertaken (i.e., the testing for convergence or inconsistency need not be described in a paper for it to have been performed by the investigators) or that the reporting of a piece of data or statistical code was not considered.

Funding statement:

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290 2007 10067 l.

Competing Interests:

The authors of this publication have no competing interests to declare.

Data Sharing:

Individual study data that has been extracted can be found by accessing the full report on the AHRQ EHC website.

Study Approval/Ethics:

This study did not include human subjects therefore ethics/institutional review board approval was not obtained.

INTRODUCTION

Clinicians and decision makers often need to select from multiple available interventions when determining the optimal treatment for a disease. Ideally, high-quality randomized controlled trials (RCTs) that estimate the effectiveness of all possible interventions directly against one another would be available to guide decision-making.[1-4] However, interventions are commonly compared with placebo or non-active control in RCTs rather than another active intervention. When direct comparative trials are completed, they typically include only two intervention from a larger group of possible treatments. As such, decision-makers are faced with a lack of adequate direct comparative data with which to make their judgments.

In the absence of head-to-head trials, indirect comparisons may provide valuable information. For example, if two different interventions have been evaluated against a common comparator, the comparative effects of the two interventions versus each other can be estimated indirectly.[1, 2] Even in the presence of head-to-head data, indirect comparisons may add value by improving precision of treatment effect estimates.

methodologies exist to indirectly compare interventions, as do modes to implement such methodologies.[1, 5-8] In the simplest form, interventions that are evaluated against a common comparator in separate trials can be compared using an anchored indirect treatment comparison approach.[5] As a generalization of indirect comparisons, when more than two treatments are being compared indirectly, and at least one pair of treatments is being compared both directly and indirectly (a closed-loop is present), both direct and indirect types of data can be used to estimate effects in a mixed treatment comparison (MTC) meta-analysis using a Bayesian or frequentist framework. [1-8] Prior research has attempted to categorize the use of indirect comparisons in the medical literature, but either did not included Bayesian MTCs or collected limited data on this approach.[9-10] The Agency for Healthcare Research and Quality commissioned us to evaluate how MTCs in published systematic reviews are conducted and reported.[11] Here, we present the findings of our systematic review identifying closed-loop MTCs using a Bayesian framework and descriptively summarize their methodological and reporting characteristics.

METHODS

A systematic literature search was conducted in MEDLINE, the Centre for Reviews and Dissemination Databases (including the Database of Abstracts and Reviews of Effects, Health Technology Assessment and the National Institute for Health Research Economic Evaluation Database), The Cochrane Library, and the American College of Physicians Journal Club from January 1, 2006 through July 31, 2011. The search strategy in **Appendix 1** was used. Manual additions were permitted based on the citations identified by the literature search.

Two independent investigators assessed citations for inclusion in a parallel manner based on *a priori* defined criteria. Specifically, we included meta-analyses that compared the clinical effectiveness or safety of interventions [any pharmacologic (including placebo and different doses), behavioral or procedural interventions] based on RCTs, utilized a Bayesian approach to conduct MTC, had at least one closed loop (**Appendix 2)** and were published in full-text and in the English language. There has been inconsistency in what constitutes a MTC in the medical literature;[12] therefore, for the purposes of this systematic review a MTC was defined as the comparison of three or more interventions in which both direct and indirect evidence was used. Methodological publications that presented MTCs for illustrative purposes and cost-effectiveness analyses were not considered in this systematic review, nor were individual patient data meta-analyses.

Two reviewers independently extracted data with disagreements resolved through discussion. For each included closed-loop Bayesian MTC, all published material including the manuscript, supplements, appendices or external websites which the reader of the article was referred to for additional information were used during data extraction. Therefore, the extraction of data was predicated on the reporting of the information by the authors within these sources. When extracting data, we recorded what the authors reported without ourselves judging whether the methods were appropriate or not. If there was insufficient data from all available sources, we indicated “not reported” for that criterion on data extraction.

General characteristics of each MTC were extracted including author and funding information, if a methodologist was an author, the number and type of intervention comparisons made, number of printed pages and use of supplement or appendix, the number of trials and patients in the analyses, clinical area (e.g., cardiology, endocrinology) and the network pattern. For the purpose of this project, we defined a methodologist as an individual having an affiliation with a department of statistics, biostatistics, epidemiology, clinical epidemiology or public health services, as determined by author information and affiliations listed in the publication.[13] The country in which a review was conducted was determined by the corresponding author’s affiliation.

The network pattern [3, 4, 11, 14] was determined by figures presented within the identified publication. If a figure was not available, we determined the pattern based on text descriptions of included trials.

We also extracted information regarding the methodology used to conduct the closed-loop Bayesian MTC including the models applied (e.g., fixed vs. random effects), description of model parameters (e.g., choices of prior distributions), methods for assessment of model fit, potential bias, inconsistency and heterogeneity, use of covariate adjustment in models, whether the model accommodated multi-arm trials, software utilized, and availability of code.

Finally, we extracted data concerning the reporting of results including the type of endpoint (e.g., binary vs. continuous), effect size and measure of variance, use of other methods to report results (e.g., probability of treatment being best, claims of equivalence or non-inferiority); and the format/presentation of results (e.g., text, tables, figures). Characteristics of the journals in which included MTCs were published were collected, including journal name, impact factor, allowance of supplements or appendices, and limitations on word, table and figure counts.

The characteristics of the closed-loop Bayesian MTCs and journals were summarized descriptively. Categorical data is presented using frequencies and continuous data as means ±standard deviations (SDs).

RESULTS

A total of 626 citations were identified through the database searches with an additional five MTCs identified through manual review (**Figure 1**). After full text review, 35 articles representing 34 unique closed-loop Bayesian MTCs were included.[15-49] The publication by Orme and colleagues[25] analyzed two distinct networks of RCTs.

The rate of publication of closed-loop Bayesian MTCs increased over the 5-year search period, with 26 (76.5%) of the MTCs published between 2009 and 2011 compared to only 8 (23.5%) published prior to 2009. On average, 6.1±4.8 authors were listed per publication and less than half of publications (47.1%) included a methodologist as an author (**Table 1**). The most common country from which authors published MTCs was the United Kingdom (35.3%), followed by the United States (11.8%) and Greece (11.8%).

Funding sources for the MTCs included governmental/foundation (29.4%), industry (26.5%) and unfunded (17.6%), with23.6% not making a statement regarding funding source(s). Only two publications identified an organizational affiliation, one each with the Health Technology Assessment Program and The Cochrane Collaboration. The mean number of printed pages per publication was 16.6±36.3 (range 4 to 221) and over half published a supplement or appendix. From those that did not publish a supplement of appendix, one publication did not have the option to do so given journal (or report) specifications.

There were 13 different categories of disease states evaluated amongst included MTCs. The mean number of interventions included within the analyses was 8.5±4.3, of which most were pharmacologic (85.7%) in nature. The mean number of trials included in the MTCs was 35.9±30.1 and the mean number of patients included was 33,459±71,233 (range 594 to 324,168).

The most common model used in closed-loop Bayesian MTCs was a random-effects model (58.5%) (**Table 2**). Very few analyses reported information about whether there was adjustment for covariates (25.6%). Of the 28 MTCs that included trials with three or more arms, 10 (35.7%) reported use of an adjustment for multi-arm trials. Less than half of all analyses reported testing model fit. Of the 15 analyses that reported testing model fit in some manner, the most common method was residual deviance (40.0%). More than two-thirds of the MTCs (76.5%) also included a traditional meta-analysis.

closed-loop Bayesian MTCs used WinBUGS software, and two also specified the use of additional software including the BUGS XLA Wrapper and S-Plus. The statistical WinBUGS code was made available to the reader in only 20.6% of cases, most often in an online supplement/appendix (71.4%). Aggregated study-level patient data used in the MTC was frequently made available to the reader and of these 21 analyses (61.8%)it was most commonly published within the manuscript itself (85.7%). Evaluation of convergence was found in 35.3% of analyses, most commonly using the Gelman-Rubin statistic (58.3%).

Utilized priors were reported as either non-informative (vague or flat) or informative in 44.1% and 8.8% of analyses, respectively. The remaining analyses (47.1%) did not specify the nature of the prior distributions used. It was also uncommon for the actual prior distribution to be reported for the population treatment effect (d) and the between-study standard deviation of population treatment differences across studies (sigma); with only 32.4% and 29.4% of MTCs, respectively, reporting this information. Sensitivity analyses based upon priors were conducted in 11.8% of MTCs.

accompanying traditional meta-analyses was common (61.5%). The most common method used to assess heterogeneity was the I^2 statistic (81.3%) followed by the Cochrane Q-statistic (43.8%). Evaluation of heterogeneity within the MTC was less common, reported in only 32.4% of publications. Of these 11 analyses, tau^2 (among-study variance of true effects) was used in 54.5% of analyses followed by between-study standard deviation (45.5%) and several other less frequent methods (some MTCs reported multiple means to test for heterogeneity and therefore are counted twice in the numerator).

Inconsistency between indirect and direct estimates was evaluated in 24 (70.6%) studies. One review reported being unable to evaluate inconsistency due to lack of direct data while the remaining MTCs simply did not comment on inconsistency. The most common method used to evaluate inconsistency was comparing results of the MTC to those of a traditional meta-analysis conducted by the authors simultaneously or a previously published traditional meta-analysis.

Most analyses (85.3%) reported outcomes that were binary **(Table 3)**. Of these 29 analyses, odds ratios were the most commonly reported effect measure (62.1%), followed by relative risks (17.2%) and hazard ratios (13.8%), among other less frequent measures. Of the 10 (29.4%) analyses that reported continuous outcomes, the weighted-mean difference was the most common effect measure (80.0%). All analyses reported variance with 95 percent credible intervals and one also reported standard errors. Most analyses did not report if the posterior distribution was the mean or median value (85.3%). Presentation of results varied, although most analyses used multiple media including tables, figures, and text.

Few analyses (8.8%) presented graphical representations of the posterior distributions of outcomes. Rank-ordering of interventions based on probability statements (including rankograms with the probability of a treatment being best, second best, and so on) for a given outcome was reported in 21 (61.8%) of the MTCs. Only one MTC made claims of equivalence and two made claims of non-inferiority, of which two defined the minimally important difference required to make these statements.

Complete details of each journal in which at least one MTC was published can be found in **Tables 4 and 5**. The 34 MTCs were published in 26 different journals, with a mean impact factor of 9.51±8.75. The British Medical Journal published the most MTCs (5 of the 34, 14.7%) followed by Current Medical Research and Opinion (4 of the 34, 11.8%). The majority of journals (73.1%) imposed word count limits and 50% imposed table/figure limitations; however, 80.8% of journals allowed online supplements or appendices.

DISCUSSION

Meta-analysis has been regarded as the most highly cited study design in health science.[50] However, a drawback of the traditional meta-analysis is its ability to compare only two interventions, without the ability to simultaneously evaluate other comparators. This is inconsistent with clinical practice as in many instances there are a variety of interventions that exist and one must decide which is best. The use of statistical methods (including simple approaches as well as MTC meta-analysis) to compare greater than two interventions simultaneously is on the rise within the peer-reviewed literature. As recent as 2005, a search of the medical literature yielded four publications that utilized such methods; while in 2011, the number increased to 57.[12] The results of our systematic review also suggest that indirect comparisons, specifically closed-loop Bayesian MTC, have become more prevalent. A recent study found that a median of 3 studies (interquartile range 2 to 6) were included per meta-analysis, with close to 75% of meta-analyses including five or less trials. [51] Our results suggest that compared to traditional meta-analyses, closed-loop Bayesian MTCs are larger and more comprehensive. Moreover, identified MTCs were published in a wide variety of journals covering a range of disease states and thus likely to reach a large readership given their collective mean impact factor. However, we found a variety of reporting strategies or a lack of reporting of characteristics that are important to the conduct of closed-loop Bayesian MTC. This may be related to the limited guidance as to how to conduct and report a MTC, a topic which has been extensively reviewed and summarized elsewhere.[11]

Prior research by Donegan and colleagues has attempted to categorize published indirect comparisons and evaluate their quality, although advanced methods including Bayesian (and frequentist) MTCs were not included.[9] Of the 43 included comparisons, 23 used an anchored indirect approach while others used hypothesis testing, confidence interval overlap, and meta-regression methods to draw indirect comparisons. The authors concluded that quality of published indirect comparisons, in particular the assessment of model assumptions and the methods used to do so, were suboptimal. A set of quality criteria were proposed by the authors to be used in future indirect comparisons, specifically evaluating if the method of indirect comparison applied was appropriate, if methods to assess similarity, homogeneity and consistency were stated and if such methods were appropriate, and details of overall interpretation and reporting of results.

Song and colleagues also have systematically reviewed previously published indirect comparisons and, of the 88 identified, found only 18 using "network or Bayesian approaches".[10] Their findings are similar to that of Donegan and colleagues, suggesting that the main methodological problems included unclear understanding of assumptions, incomplete inclusion of relevant studies, flawed or inappropriate methods, lack of similarity assessment and inappropriate combination of direct and indirect evidence.

Our systematic review adds to this existing literature by updating results and adding new information. First, the abovementioned prior reviews only included literature through 2007/2008, making ours the most up-to-date review available. Unlike prior publications, our systematic review focused only on Bayesian MTCs of networks with at least one closed loop, perhaps the most common method utilized of late to analyze complex networks of RCTs. While prior publications focused on the evaluation and reporting of assumptions made within the models, we evaluated additional model characteristics in depth including testing for model fit, evaluation of convergence, adjustment for covariates or multi-arm trials, the specific priors used and availability of the code and aggregated study-level data. Despite these differences however, our findings are consistent with prior research and with the opinion of experts regarding the challenges and concerns around implementing and reporting these more complex statistical methods.[10, 12, 52] Perhaps more clear guidance as to how to conduct and report these types of meta-analyses will lead to a more optimal and consistent approach.

While we only characterized the methods and reporting of closed-loop Bayesian MTC in this report, our search strategy was designed to capture MTCs regardless of methodological approach (including frequentist MTC). Of note, only a handful (n=9) of frequentist MTCs were identified in our search, three of which specifically reference using the methods for MTC proposed by Lumley and colleagues, while the others more generically referenced mixed-model approaches.[49, 53-60] This suggests that meta-analysts at present seem to favor a Bayesian approach to MTC, since investigators could have chosen to use either a Bayesian or Frequentist method for any of the MTC identified in our search (given all analyzed networks with at least one closed loop). Given the relative paucity of frequentist models, we do not describe the characteristics of their methods and reporting in this paper but they can be found elsewhere [11].

An important limitation of our review is that we cannot say with certainty that a lack of reporting means a given method or analysis was not undertaken (i.e., the testing for convergence or inconsistency need not be described in a paper for it to have been performed by the investigators) or that the reporting of a piece of data or statistical code was not considered. However, we evaluated word, table and figure limits imposed by journals in which these MTCs were published and our findings do not suggest journal space should be an obstacle to complete reporting. Another limitation is the definition used to describe a methodologist. While this definition has been used by previous researchers in a similar topic area [13], to our knowledge it has not been validated and therefore may not accurately depict the true involvement of an individual who considered themselves a methodologist.

With the growing publication of Bayesian MTCs in the peer-reviewed literature and the recognized challenges of such methods, its appropriate use and interpretation becomes imperative. Efforts in clarifying the appropriate use and reporting of Bayesian MTC should be of priority.

Author contributions:

DMS, JCC, CIC, WLB, OJP and CMW were responsible for study design. DMS, WLB, and OJP were responsible for data collection. DMS, CIC, JCC were responsible for data analysis and interpretation. All authors contributed to drafting the manuscript, revising the manuscript and approved the final manuscript. CIC is responsible for the overall content as the corresponding author.

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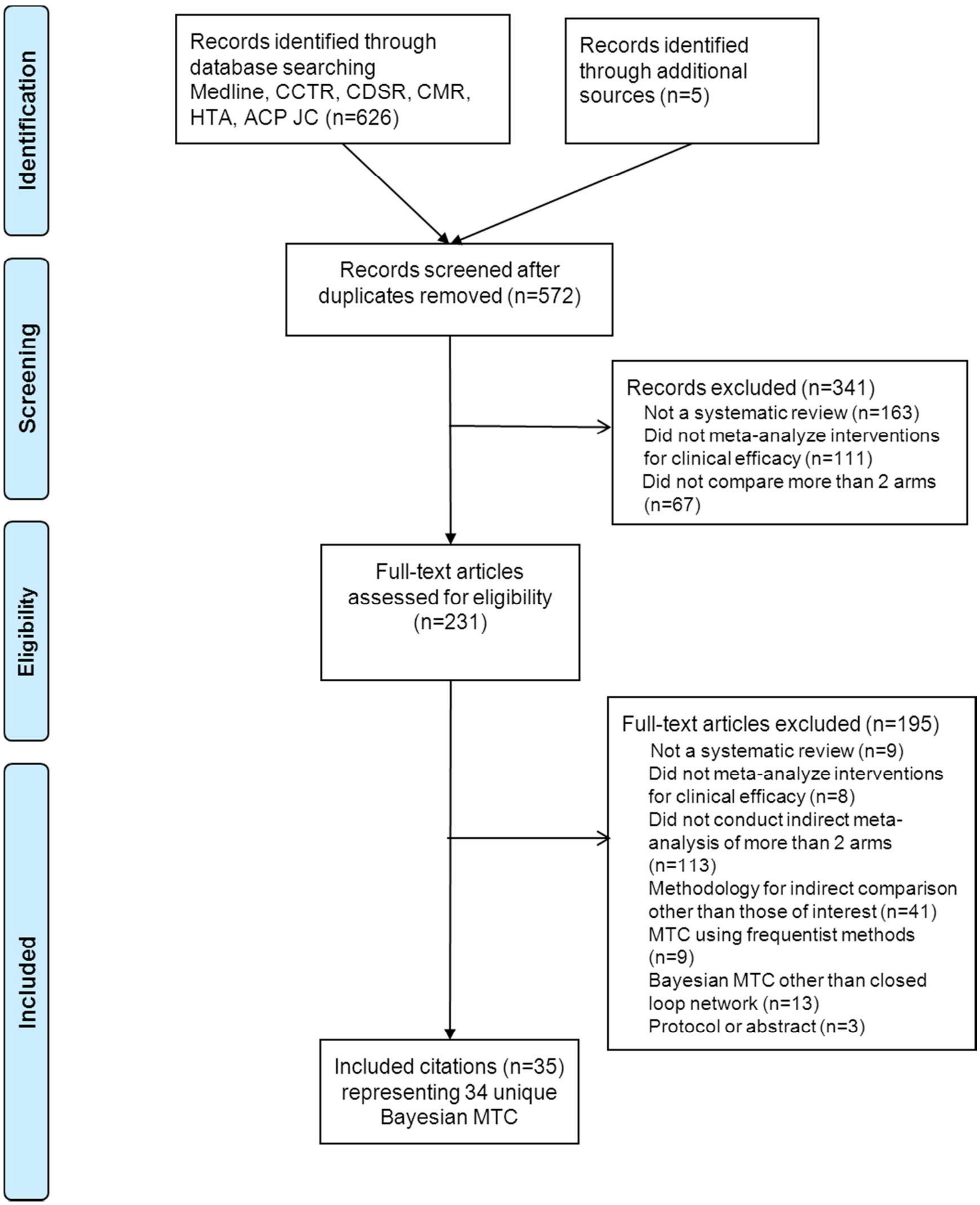
Figure 1. Flow diagram of citation inclusion and exclusion



Abbreviations: ACP JC= American College of Physicians Journal Club; CCTR=Cochrane Central Register of Controlled Trials; CDSR=Cochrane Database of Systematic Reviews; CMR=Cochrane Methodology Register; HTA=Health technology Assessment; MTC=mixed treatment comparison

Table 1. General characteristics of Bayesian mixed treatment comparisons

Characteristic	n/N (%) or Mean (SD)
Number of authors	6.1 (4.8)
Was a methodologist an author on the manuscript?	16/34 (47.1)
Country	
U.S.A.	4/34 (11.8)
United Kingdom	12/34 (35.3)
Canada	2/34 (5.9)
Brazil	1/34 (2.9)
China	2/34 (5.9)
Switzerland	3/34 (8.8)
Netherlands	1/34 (2.9)
Italy	3/34 (8.8)
Belgium	1/34 (2.9)
Greece	4/34 (11.8)
Funding	
Industry	9/34 (26.5)

Government/Foundation	10/34 (29.4)
Unfunded	6/34 (17.6)
Other	1/34 (2.9)
Not reported	8/34 (23.6)
Declared affiliation	2/34 (5.9)
Health Technology Assessment Program	1/2 (50.0)
The Cochrane Collaboration	1/2 (50.0)
Number of printed pages	16.6 (36.3)
Supplement or appendix published	20/34 (58.8)
Disease state evaluated	
Behavioral health	4/34 (11.8)
Cardiology	6/34 (17.6)
Infectious disease	2/34 (5.9)
Endocrine	2/34 (5.9)
Pulmonary	2/34 (5.9)
Pain	3/34 (8.8)
Dermatology	2/34 (5.9)

Ophthalmology	2/34 (5.9)
Rheumatology	2/34 (5.9)
Gastroenterology	3/34 (8.8)
Dental	1/34 (2.9)
Oncology	4/34 (11.8)
Substance abuse	1/34 (2.9)
Number of interventions compared*	8.5 (4.3)
Type of intervention*	
Pharmacologic	30/35 (85.7)
Devices	3/35 (8.6)
Other	1/35 (2.9)
Device and pharmacologic	1/35 (2.9)
Number of trials included in network*	35.9 (30.1)
Number of patients included in network*	33,459 (71,233)

*The trial by Orme et al. included two individual networks and they are considered separately for this characteristic

Table 2. Methods characteristics in Bayesian mixed treatment comparisons

Characteristic	**n/N (%)**
Conducted traditional meta-analysis	26/34 (76.5)
Model	
Fixed effects	1/34 (2.9)
Random effects	20/34 (58.8)
Fixed and random effects	7/34 (20.6)
Not reported	6/34 (17.6)
Adjustment for covariates	9/34 (25.6)
Adjustment for multiple arms in MTCs including trials with three or more arms	10/28 (35.7)
Model fit tested	15/34 (44.1)
Residual deviance	6/15 (40.0)
Deviance information criterion	2/15 (13.3)
Residual deviance and deviance information criterion	3/15 (20.0)
Q-Q plots	1/15 (6.7)
Mean sum deviation	1/15 (6.7)
Method not reported	2/15 (13.3)

Code published	7/34 (20.6)
Online supplement	5/7 (71.4)
External website	2/7 (28.6)
Aggregate study-level data published	21/34 (61.8)
Manuscript	18/21 (85.7)
Online supplement	2/21 (9.5)
External website	1/21 (4.8)
Evaluation of convergence*	12/34 (35.3)
Gelman Rubin statistic	7/12 (58.3)
Kernel density plot	1/12(8.3)
Visual plot inspection	1/12 (8.3)
Observation of chain mix	2/12 (16.7)
Method not reported	2/12(16.7)
Priors	
Use of noninformative	15/34 (44.1)
Use of informative priors	3/34(8.8)
Not specified	16/34 (47.1)

Prior distribution of d reported	11/34 (32.4)
Prior distribution for sigma reported	10/34(29.4)
Sensitivity analysis based on priors	4/34 (11.8)
Evaluation of heterogeneity in traditional meta-analysis*	16/26(61.5)
I^2	13/16 (81.3)
Cochrane-Q statistic	7/16 (43.8)
PICO statement	1/16(6.3)
Plot visualization	2/16 (12.5)
L'Abbe plot	1/16 (6.3)
Evaluation of heterogeneity in network meta-analysis*	11/34(32.4)
Precision (tau^2)	6/11 (54.5)
Between study SD	5/11(45.5)
Heterogeneity p-values	1/11 (9.1)
Evaluation of inconsistency*	24/34 (70.6)
Comparison to traditional or prior meta-analysis†	12/24 (50.0)
Inconsistency/incoherence factors	4/12 (33.3)
Posterior mean residual deviance	3/12 (25.0)

Method not reported	4/12 (33.3)
Trial sequential analysis	1/12 (8.3)
Overall inconsistency ($\sigma^2 w$)	1/12 (8.3)

*Studies that used multiple methods to test heterogeneity were counted multiple times, in the respective categories
†Authors either compared results of the MTC to a traditional meta-analysis that they conducted concurrently or to a traditional meta-analysis that was previously published

Abbreviations: MTC=mixed treatment comparison; PICO=patient, intervention, comparator, outcome; SD=standard deviation

Table 3. Outcomes and results reporting in Bayesian mixed treatment comparisons

Characteristic	n/N (%) or Mean (SD)
Graphical representation of posterior distribution	3/34 (8.8)
Ranking of outcomes	21/34 (61.8)
Claims of equivalence	1/34 (2.9)
Claims of non-inferiority	2/34 (5.9)
Minimally important difference	8/47 (17.0)
Type of outcome	
Binary	23/34 (67.6)
Continuous	4/34 (11.8)
Binary and continuous	6/34 (17.6)
Categorical non-binary	1/34 (2.9)
Binary effect measure	29/34 (85.3)
Relative risk	5/29 (17.2)
Odds ratio	18/29 (62.1)
Hazard ratio	4/29 (13.8)
Multiple effect measures	2/39 (6.9)

Continuous effect measure	10/34 (29.4)
Weighted mean difference	8/10 (80.0)
Multiple	2/10 (20.0)
Categorical non-binary effect measure	1/34 (2.9)
Relative risk	1/1 (100)
Presentation of Results*	
Table	24/34 (70.6)
Text	32/34 (94.1)
Figure	21/34 (61.8
Posterior distribution	
Mean	1/34 (2.9)
Median	4/34 (11.8)
Not reported	29/34 (85.3)

*Studies were counted multiple times when more than one method was used.

Table 4. Aggregate journal characteristics

Characteristics	**Yes n/N (%) or Mean (SD)**
Impact factor	9.51 (8.75)
Supplement or appendix allowed	21/26 (80.8)
Online	19/21 (90.5)
Not specified	2/21 (9.5)
Word count limit	19/26 (73.1)
Table count limit	13/26 (50.0)
Figure count limit	13/26 (50.0)

Table 5. Individual journal characteristics

Journal	Included studies	Impact factor*	Supplement or appendix; format	Word count limit	Table limit	Figure limit
Alimentary Pharmacology & Therapeutics	Edwards, 2009a	3.861	Y, online	N	N	N
Annals of Internal Medicine	Gross, 2011	16.792	Y, not specified	3,500-4,000	4 tables or figures	4 tables or figures
Archives of Internal Medicine	Sciarretta, 2011; Cooper, 2006	10.639	Y, online	3,500	6 to 8 tables or figures	6 to 8 tables or figures
British Medical Journal	Baldwin, 2011; Hartling, 2011; Trelle, 2011; Wandel, 2010; Lam, 2007	13.471	Y, online	N	N	N
British Journal of Anaesthesia	Maund, 2011†	4.224	Y, online	5,000	N	N

Journal	Included studies	Impact factor*	Supplement or appendix; format	Word count limit	Table limit	Figure limit
British Journal of Cancer	Coon, 2009	4.831	Y, online	5,000-5,500	1 table reduces word limit by 200	1 figure reduces word limit by 200
British Journal of Ophthalmology	Van den Bruel, 2011	2.934	Y, online	3,000	5 tables or figures	5 tables or figures
Cancer Treatment Reviews	Golfinopoulus, 2009	6.811	N	N	N	N
Clinical Therapeutics	Edwards, 2009b	2.551	Y, online	5,500-6,000	N	N
Cochrane Database of Systematic Reviews	Walsh, 2010	6.186	N	N	N	N
Current Medical Research and Opinion	van de Kerkhof, 2011; Orme, 2010; Uthman, 2010; Vissers, 2010	2.609*	Y, online	11,200	N	N

Journal	Included studies	Impact factor*	Supplement or appendix; format	Word count limit	Table limit	Figure limit
Dermatology	Bansback, 2009	2.714	Y, not specified	13 pages for text, tables, figures	Included in page count	Included in page count
Drug and Alcohol Dependence	Meader, 2009	3.365	Y, online	6,000	N	N
Gastroenterology	Woo, 2010	12.023	Y, online	6,000	Minimum of 4 to 6 figures or illustrations	Minimum of 4 to 6 figures or illustrations
Health technology assessment (Winchester, England)	Maund, 2011†	4.197	N	N	N	N
The Journal of the American Medical Association	Phung, 2010	30	Y, online	3,500	4 tables or figures	4 tables or figures

Journal	Included studies	Impact factor*	Supplement or appendix; format	Word count limit	Table limit	Figure limit
Journal of Hospital Infection	Wang, 2010	3.078	N	5,000	N	N
Journal of Hypertension	Coleman, 2008	3.98	Y, online	N	N	N
Journal of the National Cancer Institute	Mauri, 2008; Kyrgiou, 2006	14.697	Y, online	6,000	8 table or figures	8 tables or figures
Lancet	Cipriani, 2009l Stettler, 2007	33.633	Y, online	4,500	"Should include about 5 illustrations"	"Should include about 5 illustrations"
Lancet Infectious Disease	Manzoli, 2009	16.144	Y, online	3,000-5,000	"Should include about 5 illustrations"	"Should include about 5 illustrations"
Lancet Neurology	Bangalore, 2011	21.659	Y, online	3,000-4,500	"Should include about 5 illustrations"	"Should include about 5 illustrations"

Journal	Included studies	Impact factor*	Supplement or appendix; format	Word count limit	Table limit	Figure limit
Lancet Oncology	Golfinopoulos, 2007	17.764	Y, online	3,000-5,000	"Should include about 5-6 illustrations"	"Should include about 5-6 illustrations"
Pharmacotherapy	Baker, 2009	2.631	N	7,000	N	N
Rheumatology	Nixon, 2007	4.171	Y, online	3,500	6 figures or tables	6 figures or tables
Value in Health	Dakin, 2010	2.342	Y, online	N	N	N

Abbreviations: Y: yes; N: no

*: The impact factor was obtained from Web of Science in 2012, except when the symbol appears for that journal the impact factor was not available in Web of Science and was taken from the journal's website.

†: Published as a manuscript and health technology assessment report, but counted as one unique publication

Methods Used to Conduct and Report Closed Loop Bayesian Mixed Treatment Comparisons Published in the Medical Literature: A Systematic Review

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Figures: 1

Appendices: 2

ABSTRACT

Objectives: To identify published closed-loop Bayesian mixed treatment comparisons (MTCs) and to summarize characteristics regarding their conduct~~ion~~ and reporting.

Design: Systematic review.

Methods: We searched multiple bibliographic databases (January 2006-July 31, 2011) for full-text, English language publications of Bayesian MTCs comparing the effectiveness or safety of ≥3 interventions based on randomized controlled trials and having at least one closed loop. Methodological and reporting characteristics of MTCs were extracted in duplicate and summarized - descriptively.

Results: We identified 34 Bayesian MTCs spanning 13 clinical areas. Publication of MTCs increased over the 5-year period; with 76.5% published during or after 2009. MTCs included a mean (± standard deviation) of 35.9±30.1 trials (n=33,459±71,233 subjects) and 8.5±4.3 interventions (85.7 % pharmacologic). Non-informative and informative prior distributions were reported to be used in 44.1% and 8.8% of MTCs; respectively, with the remainder failing to specify the prior used. A random-effects model was used to analyze the networks of trials in 58.5% of MTCs, all using WinBUGS; however, code was infrequently provided (20.6%). More than two-thirds of MTCs (76.5%) also conducted traditional meta-analysis. Methods used to evaluate ~~of~~ convergence, heterogeneity and inconsistency were infrequently reported, but from those providing detail, methods appeared varied. MTCs most often used a binary effect measure (85.3%) and ranking of interventions based upon probability was common (61.8%), although rarely displayed~~one~~ in a figure (8.8% of MTCs). MTCs were published in 26 different journals with a mean impact factor of 9.51±8.75. While 73.1% of journals imposed limits on word counts and 50% limits on the number of tables/figures, online supplements/appendices were allowed in 80.8% of journals.

~~**Conclusion:**~~ Publication of closed-loop Bayesian MTCs is increasing in frequency, but details regarding their methodology are often poorly described. Efforts in clarifying the appropriate methods and reporting of Bayesian MTCs should be of priority. ~~to thought leaders.~~

Word count: ~~296~~ 294 of 300

Article Summary

Article focus

- To identify published closed-loop Bayesian mixed treatment comparisons (MTCs) and to summarize characteristics regarding their conduct~~ion~~ and reporting.

Key messages

- We identified 34 closed-loop Bayesian MTCs spanning 13 clinical areas, published in 26 different journals.
- ~~Publication of~~ closed-loop Bayesian MTCs is increasing in frequency, but details regarding their methodology are often poorly described. Efforts in clarifying the appropriate methods and reporting of Bayesian MTCs should be of priority. ~~to thought leaders.~~

Strengths and limitations of this study

- Our systematic review adds to this existing literature by updating results and adding new information as prior reviews only included literature through 2007/2008. Unlike prior publications, our systematic review focused only on Bayesian MTCs of networks with at least one closed loop.
- Unlike prior reviews, we evaluated reporting of additional model characteristics in depth including testing for model fit, evaluation of convergence, adjustment for covariates or multi-arm trials, the specific priors used and availability of the code and aggregated study-level data.
- An important limitation of our review is that we cannot say with certainty that a lack of reporting means a given method or analysis was not undertaken (i.e., the testing for convergence or inconsistency need not be described in a paper for it to have been performed by the investigators) or that the reporting of a piece of data or statistical code was not considered.

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Competing Interests:

The authors of this publication have no competing interests to declare.

Data Sharing:

Individual study data that has been extracted can be found by accessing the full report on the AHRQ EHC website.

Study Approval/Ethics:

This study did not include human subjects therefore ethics/institutional review board approval was not obtained.

INTRODUCTION

Clinicians and decision makers often ~~have~~ need to select from multiple available interventions when determining the optimal treatment for a disease. Ideally, high-quality randomized controlled trials (RCTs) that estimate the effectiveness of all possible interventions directly against one another would be available to guide decision-making.[1-4] However, interventions are commonly compared with placebo or non-active control in RCTs rather than another active intervention.~~,~~ ~~and~~ W~~w~~hen direct comparative trials are completed, they ~~are~~typically include~~exist they are between~~ only two intervention from~~s~~ a larger group of possible treatments. As such, decision-makers are faced with a lack of adequate direct comparative data with which to make their judgments.

In the absence of ~~direct comparative data~~head-to-head ~~studies~~trials, indirect comparisons may provide valuable information. For example, if two different interventions have been evaluated against a common comparator, the comparative effects of the two interventions ~~compared with~~versus each other can be estimated indirectly.[1, 2] Even in the presence of ~~direct comparative~~head-to-head data, indirect comparisons may add value ~~to the interpretation of comparative effectiveness~~ by improving precision of treatment effect estimates.

~~Several~~ methodologies exist to indirectly compare interventions, as do modes to implement such methodologies.[1, 5-8] In the simplest form, interventions that are evaluated against a common comparator in separate trials can be compared ~~to each other indirectly~~ using an anchored indirect treatment comparison approach.[5] As a generalization of indirect comparisons, when more than two treatments are being compared indirectly, and at least one pair of treatments is being compared both directly and indirectly (a closed-loop is present), both direct and indirect types of data can be used to estimate effects in a mixed treatment comparison (MTC) meta-analysis using a Bayesian or frequentist framework. [1-8] Prior research has attempted to categorize the use of indirect comparisons in the medical literature, but either did not included Bayesian MTCs or collected limited data on this approach.[9-10] The Agency for Healthcare Research and Quality commissioned us to evaluate how MTCs in published systematic reviews are conducted and reported.[11] Here, we present the findings of our systematic review ~~from this report~~ identifying closed-loop MTCs using a Bayesian framework and descriptively summarize their methodological and reporting characteristics.

METHODS

A systematic literature search was conducted in MEDLINE, the Centre for Reviews and Dissemination Databases (including the Database of Abstracts and Reviews of Effects, Health Technology Assessment and the National Institute for Health Research Economic Evaluation Database), The Cochrane Library, and the American College of Physicians Journal Club from January 1, 2006 through July 31, 2011. The search strategy in **Appendix 1** was used. Manual additions were permitted based on the citations identified by the literature search.

Two independent investigators assessed citations for inclusion in a parallel manner based on *a priori* defined criteria. Specifically, we included meta-analyses that compared the clinical effectiveness or safety of interventions [any pharmacologic (including placebo and different doses), behavioral or procedural interventions] based on RCTs, utilized a Bayesian approach to conduct MTC, had at least one closed loop (**Appendix 2**) and were published in full-text and in the English language. There has been inconsistency in what constitutes a MTC in the medical literature;[12~~1~~] therefore, for the purposes of this systematic review a MTC was defined as the comparison of three or more interventions ~~and a network pattern that~~ in which both direct and indirect evidence was used~~contained at least one closed loop (**Appendix 2**)~~. Methodological publications that presented MTCs for illustrative purposes and cost-effectiveness analyses were not considered in this systematic review, nor were individual patient data meta-analyses.

Two reviewers independently extracted data with disagreements resolved through discussion. For each included closed-loop Bayesian MTC, all published material including the manuscript, supplements, appendices or external websites which the reader of the article was referred to for additional information were used during data extraction. Therefore, the extraction of data was predicated on the reporting of the information by the authors within these sources. When extracting data, we recorded what the authors reported without ourselves judging whether the methods were appropriate or not. If there was insufficient data from all available sources, we indicated "not reported" for that criterion on data extraction.

General characteristics of each MTC were extracted including author and funding information, if a methodologist was an author, the number and type of intervention comparisons made, number of printed pages and use of supplement or appendix, the number of trials and patients in the analyses, clinical area (e.g., cardiology, endocrinology) and the network pattern. For the purpose of this project, we defined a methodologist as an individual having an affiliation with a department of statistics, biostatistics, epidemiology, clinical epidemiology or public health services, as determined by author information and affiliations listed in the publication.[13~~2~~] The country in which a review was conducted was determined by the corresponding author's affiliation.

The network pattern [3, 4, 11, 14~~3, 14~~] was determined by figures presented within the identified publication. If a figure was not available, we ~~as investigators~~ determined the pattern based on text descriptions of included trials.

We also extracted information regarding the methodology used to conduct the closed-loop Bayesian MTC including the models applied (e.g., fixed vs. random effects), description of model parameters (e.g., choices of prior distributions), methods for assessment of model fit, potential bias, inconsistency and heterogeneity, use of covariate adjustment in models, whether the model accommodated multi-arm trials, software utilized, and availability of code.

Finally, we extracted data concerning the reporting of results including the type of endpoint (e.g., binary vs. continuous), effect size and measure of variance, use of other methods to report results (e.g., probability of treatment being best, claims of equivalence or non-inferiority); and the format/presentation of results (e.g., text, tables, figures). Characteristics of the journals in which included MTCs were published were collected, including journal name, impact factor, allowance of supplements or appendices, and limitations on word, table and figure counts.

The characteristics of the closed-loop Bayesian MTCs and journals were summarized descriptively. Categorical data is presented using frequencies and continuous data as means ±standard deviations (SDs).

RESULTS

A total of 626 citations were identified through the database searches with an additional five MTCs identified through manual review (**Figure 1**). After full text review, 35 articles representing 34 unique closed-loop Bayesian MTCs were included.[15-49] The publication by Orme and colleagues[25] analyzed two distinct networks of RCTs.

The rate of publication of closed-loop Bayesian MTCs increased over the 5-year search period, with 26 (76.5%) of the MTCs published between 2009 and 2011 compared to only 8 (23.5%) published prior to 2009. On average, 6.1±4.8 authors were listed per publication and less than half of publications (47.1%) included a methodologist as an author (**Table 1**). The most common country from which authors published MTCs was the United Kingdom (35.3%), followed by the United States (11.8%) and Greece (11.8%). ~~The remaining analyses were published by authors based in a variety of countries.~~

Funding sources for the MTCs included governmental/foundation (29.4%), industry (26.5%) and unfunded (17.6%), with23.6% not making a statement regarding funding source(s). Only two ~~analyses~~ publications identified an organizational affiliation, one each with the Health Technology Assessment Program and The Cochrane Collaboration. The mean number of printed pages per ~~MTC~~ publication was 16.6±36.3 (range 4 to 221) and over half published a supplement or appendix. From those that did not publish a supplement of appendix, one ~~Only one~~ publication ~~from those that did not publish a supplement or appendix~~ did not have the option to do so given journal (or report) specifications.

There were 13 different categories of disease states evaluated amongst included MTCs. ~~in identified closed-loop Bayesian MTCs.~~ The mean number of interventions included within the analyses was 8.5±4.3, of which most were pharmacologic (85.7%) in nature. The mean number of trials included in the MTCs was 35.9±30.1 and the mean number of patients included was 33,459±71,233 (range 594 to 324,168).

The most common model used in closed-loop Bayesian MTCs was a random-effects model (58.5%) (**Table 2**). Very few analyses reported information about whether there was adjustment for covariates (25.6%). Of the 28 MTCs that included trials with three or more arms, 10 (35.7%) ~~analyses~~ reported use of an adjustment for multi-arm trials. Less than half of all~~the~~ analyses reported testing ~~the~~ model fit. Of the 15 analyses that reported testing model fit in some manner, the most common method was ~~use of~~ residual deviance (40.0%). More than two-thirds of the ~~Bayesian~~ MTCs (76.5%) also included a traditional meta-analysis.

~~All~~ closed-loop Bayesian MTCs used WinBUGS software, and two also specified the use of additional software including the BUGS XLA Wrapper and S-Plus. The statistical WinBUGS code was made available to the reader in only 20.6% of cases, most often ~~and, of these, it was most often found~~ in an online supplement/appendix (71.4%). Aggregated study-level patient data used in the MTC was frequently made available to the reader~~,~~ and of these 21 analyses (61.8%) ~~that published such data,~~ it was most commonly published within ~~found in the~~the manuscript itself (85.7%). Evaluation of convergence was found in 35.3% of analyses, most commonly using the ~~and, of these, the most common method was the~~ Gelman-Rubin statistic (58.3%). ~~, although several less frequent methods were used as well.~~

Utilized priors were reported as either non-informative (vague or flat) or informative in 44.1% and 8.8% of analyses, respectively. The remaining analyses (47.1%) did not specify the nature of the prior distributions used. It was also uncommon for the actual prior distribution to be reported for the population treatment effect (d) and the between-study standard deviation of population treatment differences across studies (sigma); with only 32.4% and 29.4% of MTCs, respectively, reporting this information. Sensitivity analyses based upon priors were conducted in 11.8% of MTCs.

~~Evaluation of heterogeneity within~~ accompanying traditional meta-analyses was common (61.5%). The most common method used to assess heterogeneity was the I^2 statistic (81.3%) followed by the Cochrane Q-statistic (43.8%).~~, among many less frequent methods.~~ Evaluation of heterogeneity within the MTC was less common, reported in only 32.4% of publications. Of these 11 analyses, tau^2 (among-study variance of true effects) was used in 54.5% of analyses followed by between-study standard deviation (45.5%) and several other less frequent methods (some MTCs reported multiple means to test for heterogeneity and therefore are counted twice in the numerator).

Inconsistency between indirect and direct estimates was evaluated in 24 (70.6%) studies. One review reported being unable to evaluate inconsistency due to lack of direct data while the remaining MTCs simply did not comment on inconsistency. The most common method used to evaluate inconsistency was comparing results of the MTC to those of ~~with either~~ a traditional meta-analysis conducted by the authors simultaneously or a previously published traditional meta-analysis.

Most analyses (85.3%) reported outcomes that were binary **(Table 3)**. Of these 29 analyses, odds ratios were the most commonly reported effect measure (62.1%), followed by relative risks (17.2%) and hazard ratios (13.8%), among other less frequent measures. Of the 10 (29.4%) analyses that reported continuous outcomes, the weighted-mean difference was the most common effect measure (80.0%). All analyses reported variance with 95 percent credible intervals and one also reported standard errors. Most analyses did not report if the posterior distribution was the mean or median value

(85.3%). Presentation of results ~~data~~ varied, although most analyses used multiple media including tables, figures, and text.

Few analyses (8.8%) presented graphical representations of the posterior distributions of outcomes. Rank-ordering of interventions based on probability statements (including rankograms with the probability of a treatment being best, second best, and so on) for a given outcome was reported in 21 (61.8%) of the MTCs. Only one MTC made claims of equivalence and two made claims of non-inferiority, of which ~~and of these,~~ two defined the minimally important difference required to make these statements~~is determination~~.

Complete details of each journal in which at least one MTC was published can be found in **Tables 4 and 5**. The 34 MTCs were published in 26 different journals, with a mean impact factor of 9.51±8.75. The British Medical Journal published the most ~~Bayesian~~ MTCs (5 of the 34, 14.7%) followed by Current Medical Research and Opinion (4 of the 34, 11.8%). The majority of journals (73.1%) imposed word count limits and 50% imposed table/figure limitations; however, 80.8% of journals allowed online supplements or appendices.

DISCUSSION

Meta-analysis has been regarded as the most highly cited study design in health science.[50] However, a drawback of the traditional meta-analysis is its ability to compare only two interventions, without the ability to simultaneously evaluate other comparators. This is inconsistent with clinical practice as in many instances there are a variety of interventions that exist and one must decide which is best. The use of statistical methods (including simple approaches as well as MTC meta-analysis) to compare greater than two interventions simultaneously is on the rise within the peer-reviewed literature. As recent as 2005, a search of the medical literature yielded four publications that utilized such methods; while in 2011, the number increased to 57.[12~~1~~] The results of our systematic review also suggest that indirect comparisons, specifically closed-loop Bayesian MTC, have become more prevalent. A recent study found that a median of 3 studies (interquartile range 2 to 6) were included per meta-analysis, with close to 75% of meta-analyses including five or less trials. [51] Our results suggest that compared to traditional meta-analyses, closed-loop Bayesian MTCs are larger and more comprehensive. Moreover, identified MTCs were published in a wide variety of journals covering a range of disease states and thus likely to reach a large readership given their collective mean impact factor. However, we found a variety of reporting strategies or a lack of reporting of characteristics that are important to the conduct of closed-loop Bayesian MTC. This may be related to the limited guidance as to how to conduct and report a MTC, a topic which has been extensively reviewed and summarized elsewhere.[11]

~~Bayesian MTCs are often criticized for requiring the use of prior information (which is most commonly non-informative) and its need to be run with non-user friendly software.[14] Despite this fact, a recently published survey of Cochrane systematic review authors found that most accept indirect evidence as a source of data comparing relative effectiveness of interventions.[51] Although many of the authors had some knowledge of indirect comparison methods, the majority reported never having used such methods and felt they needed more training in this field. To date, there seems to be only limited guidance as to how to conduct and report a MTC,[14] creating an environment of inconsistency in the literature.~~

Prior research by Donegan and colleagues has attempted to categorize published indirect comparisons and evaluate their quality, although advanced methods including Bayesian (and frequentist) MTCs were not included.[9] Of the 43 included comparisons, 23 used an anchored indirect approach while others used hypothesis testing, confidence interval overlap, and meta-regression methods to draw indirect comparisons. The authors concluded that quality of published indirect comparisons, in particular the assessment of model assumptions and the methods used to do so, were suboptimal. A set of quality criteria were proposed by the authors to be used in future indirect comparisons, specifically evaluating if the method of indirect comparison applied was appropriate, if methods to assess similarity, homogeneity and consistency were stated and if such methods were appropriate, and details of overall interpretation and reporting of results.

Song and colleagues also have systematically reviewed previously published indirect comparisons and, of the 88 identified, found only 18 using “network or Bayesian approaches”.[10] Their findings are similar to that of Donegan and colleagues, suggesting that the main methodological problems included unclear understanding of assumptions, incomplete inclusion of relevant studies, flawed or inappropriate methods, lack of similarity assessment and inappropriate combination of direct and indirect evidence.

Our systematic review adds to this existing literature by updating results and adding new information. First, the abovementioned prior reviews only included literature through 2007/2008, making ours the most up-to-date review available. Unlike prior publications, our systematic review focused only on Bayesian MTCs of networks with at least one closed loop, perhaps the most common method utilized of late to analyze complex networks of RCTs. While prior publications focused on the evaluation and reporting of assumptions made within the models, we evaluated additional model characteristics in depth including testing for model fit, evaluation of convergence, adjustment for covariates or multi-arm trials, the specific priors used and availability of the code and aggregated study-level data. Despite these differences however, our findings are consistent with prior research and with the opinion of experts regarding the challenges and concerns around implementing and reporting these more complex statistical methods.[10, 12~~1~~, 52] Perhaps more clear guidance as to how to conduct and report these types of meta-analyses will lead to a more optimal and consistent approach.

While we only characterized the methods and reporting of closed-loop Bayesian MTC in this report, our search strategy was designed to capture MTCs regardless of methodological approach (including frequentist MTC). Of note, only a handful (n=9) of frequentist MTCs were identified in our search, three of which specifically reference using the methods for MTC proposed by Lumley and colleagues, while the others more generically referenced mixed-model approaches.[49, 53-60] This suggests that meta-analysts at present seem to favor a Bayesian approach to MTC, since investigators could have chosen to use either a Bayesian or Frequentist method for any of the MTC identified in our search (given all analyzed networks with at least one closed loop). Given the relative paucity of frequentist models, we do not describe the characteristics of their methods and reporting in this paper but they can be found elsewhere [11~~4~~].

An important limitation of our review is that we cannot say with certainty that a lack of reporting means a given method or analysis was not undertaken (i.e., the testing for convergence or inconsistency need not be described in a paper for it to have been performed by the investigators) or that the reporting of a piece of data or statistical code was not considered. However, we evaluated word, table and figure limits imposed by journals in which these MTCs were published and our findings do not suggest journal space should be an obstacle to complete reporting. Another limitation is the definition used to describe a methodologist. While this definition has been used by previous researchers in a similar topic area [13], to our knowledge it has not been validated and therefore may not accurately depict the true involvement of an individual who considered themselves a methodologist.

With the growing publication of Bayesian MTCs in the peer-reviewed literature and the recognized challenges of such methods, ~~the~~ its appropriate use~~ of this methodology~~ and interpretation ~~of such work~~ becomes imperative. Efforts in clarifying the appropriate use and reporting of Bayesian MTC should be of priority.~~ to thought leaders.~~

Author contributions:

DMS, JCC, CIC, WLB, OJP and CMW were responsible for study design. DMS, WLB, and OJP were responsible for data collection. DMS, CIC, JCC were responsible for data analysis and interpretation. All authors contributed to drafting the manuscript, revising the manuscript and approved the final manuscript. CIC is responsible for the overall content as the corresponding author.

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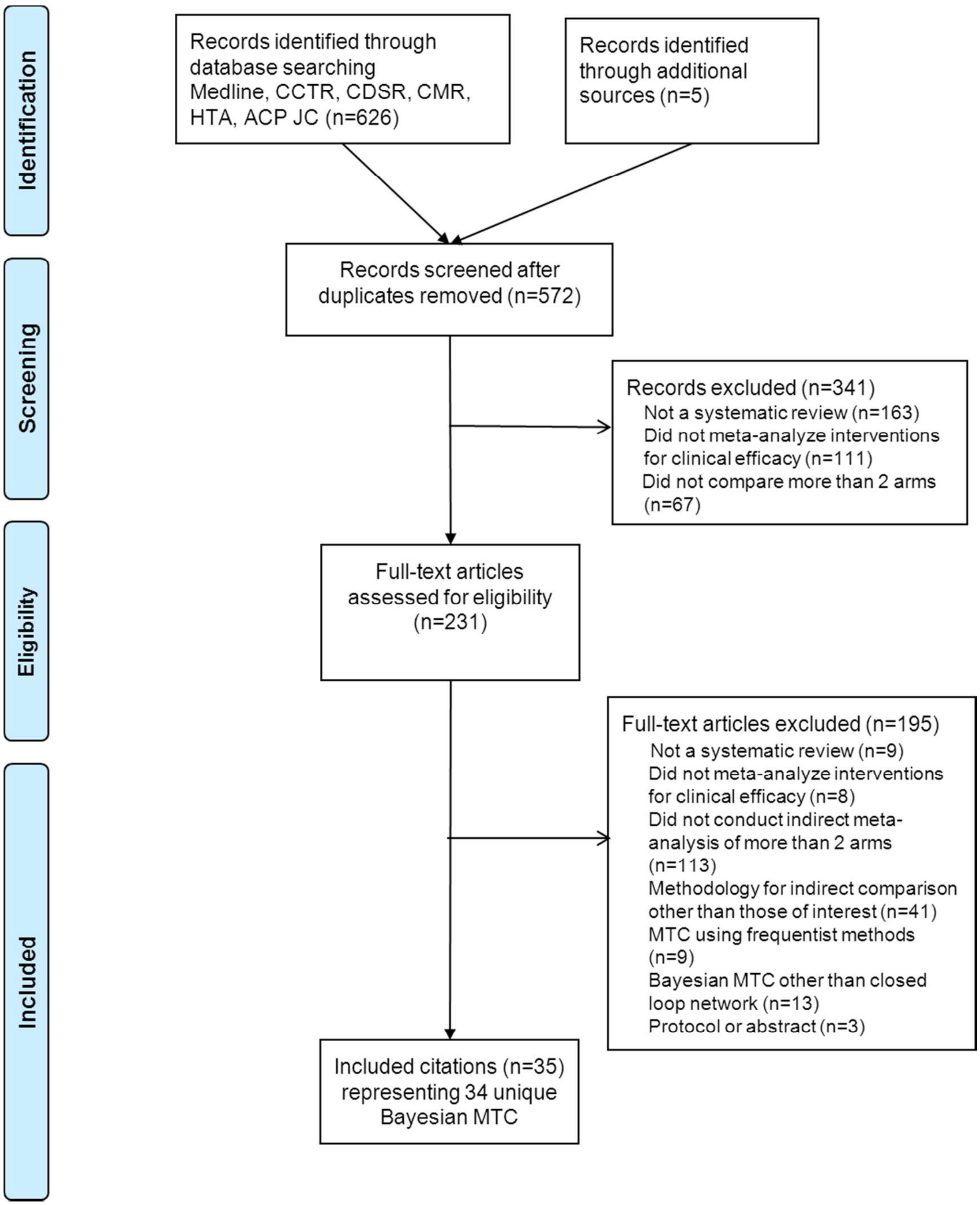
Figure 1. Flow diagram of citation inclusion and exclusion



Abbreviations: ACP JC= American College of Physicians Journal Club; CCTR=Cochrane Central Register of Controlled Trials; CDSR=Cochrane Database of Systematic Reviews; CMR=Cochrane Methodology Register; HTA=Health technology Assessment; MTC=mixed treatment comparison

Table 1. General characteristics of Bayesian mixed treatment comparisons

Characteristic	n/N (%) or Mean (SD)
Number of authors	6.1 (4.8)
Was a methodologist an author on the manuscript?	16/34 (47.1)
Country	
U.S.A.	4/34 (11.8)
United Kingdom	12/34 (35.3)
Canada	2/34 (5.9)
Brazil	1/34 (2.9)
China	2/34 (5.9)
Switzerland	3/34 (8.8)
Netherlands	1/34 (2.9)
Italy	3/34 (8.8)
Belgium	1/34 (2.9)
Greece	4/34 (11.8)
Funding	
Industry	9/34 (26.5)

Government/Foundation	10/34 (29.4)
Unfunded	6/34 (17.6)
Other	1/34 (2.9)
Not reported	8/34 (23.6)
Declared affiliation	2/34 (5.9)
Health Technology Assessment Program	1/2 (50.0)
The Cochrane Collaboration	1/2 (50.0)
Number of printed pages	16.6 (36.3)
Supplement or appendix published	20/34 (58.8)
Disease state evaluated	
Behavioral health	4/34 (11.8)
Cardiology	6/34 (17.6)
Infectious disease	2/34 (5.9)
Endocrine	2/34 (5.9)
Pulmonary	2/34 (5.9)
Pain	3/34 (8.8)
Dermatology	2/34 (5.9)

Ophthalmology	2/34 (5.9)
Rheumatology	2/34 (5.9)
Gastroenterology	3/34 (8.8)
Dental	1/34 (2.9)
Oncology	4/34 (11.8)
Substance abuse	1/34 (2.9)
Number of interventions compared*	8.5 (4.3)
Type of intervention*	
Pharmacologic	30/35 (85.7)
Devices	3/35 (8.6)
Other	1/35 (2.9)
Device and pharmacologic	1/35 (2.9)
Number of trials included in network*	35.9 (30.1)
Number of patients included in network*	33,459 (71,233)

*The trial by Orme et al. included two individual networks and they are considered separately for this characteristic

Table 2. Methods characteristics in Bayesian mixed treatment comparisons

Characteristic	**n/N (%)**
Conducted traditional meta-analysis	26/34 (76.5)
Model	
Fixed effects	1/34 (2.9)
Random effects	20/34 (58.8)
Fixed and random effects	7/34 (20.6)
Not reported	6/34 (17.6)
Adjustment for covariates	9/34 (25.6)
Adjustment for multiple arms in MTCs including trials with three or more arms	10/28 (35.7)
Model fit tested	15/34 (44.1)
Residual deviance	6/15 (40.0)
Deviance information criterion	2/15 (13.3)
Residual deviance and deviance information criterion	3/15 (20.0)
Q-Q plots	1/15 (6.7)
Mean sum deviation	1/15 (6.7)
Method not reported	2/15 (13.3)

Code published	7/34 (20.6)
Online supplement	5/7 (71.4)
External website	2/7 (28.6)
Aggregate study-level data published	21/34 (61.8)
Manuscript	18/21 (85.7)
Online supplement	2/21 (9.5)
External website	1/21 (4.8)
Evaluation of convergence*	12/34 (35.3)
Gelman Rubin statistic	7/12 (58.3)
Kernel density plot	1/12(8.3)
Visual plot inspection	1/12 (8.3)
Observation of chain mix	2/12 (16.7)
Method not reported	2/12(16.7)
Priors	
Use of noninformative	15/34 (44.1)
Use of informative priors	3/34(8.8)
Not specified	16/34 (47.1)

Prior distribution of d reported	11/34 (32.4)
Prior distribution for sigma reported	10/34(29.4)
Sensitivity analysis based on priors	4/34 (11.8)
Evaluation of heterogeneity in traditional meta-analysis*	16/26(61.5)
I^2	13/16 (81.3)
Cochrane-Q statistic	7/16 (43.8)
PICO statement	1/16(6.3)
Plot visualization	2/16 (12.5)
L'Abbe plot	1/16 (6.3)
Evaluation of heterogeneity in network meta-analysis*	11/34(32.4)
Precision (tau^2)	6/11 (54.5)
Between study SD	5/11(45.5)
Heterogeneity p-values	1/11 (9.1)
Evaluation of inconsistency*	24/34 (70.6)
Comparison to traditional or prior meta-analysis†	12/24 (50.0)
Inconsistency/incoherence factors	4/12 (33.3)
Posterior mean residual deviance	3/12 (25.0)

Method not reported	4/12 (33.3)
Trial sequential analysis	1/12 (8.3)
Overall inconsistency (σ^2w)	1/12 (8.3)

*Studies that used multiple methods to test heterogeneity were counted multiple times, in the respective categories
†Authors either compared results of the MTC to a traditional meta-analysis that they conducted concurrently or to a traditional meta-analysis that was previously published

Abbreviations: MTC=mixed treatment comparison; PICO=patient, intervention, comparator, outcome; SD=standard deviation

Table 3. Outcomes and results reporting in Bayesian mixed treatment comparisons

Characteristic	n/N (%) or Mean (SD)
Graphical representation of posterior distribution	3/34 (8.8)
Ranking of outcomes	21/34 (61.8)
Claims of equivalence	1/34 (2.9)
Claims of non-inferiority	2/34 (5.9)
Minimally important difference	8/47 (17.0)
Type of outcome	
Binary	23/34 (67.6)
Continuous	4/34 (11.8)
Binary and continuous	6/34 (17.6)
Categorical non-binary	1/34 (2.9)
Binary effect measure	29/34 (85.3)
Relative risk	5/29 (17.2)
Odds ratio	18/29 (62.1)
Hazard ratio	4/29 (13.8)
Multiple effect measures	2/39 (6.9)

Continuous effect measure	10/34 (29.4)
Weighted mean difference	8/10 (80.0)
Multiple	2/10 (20.0)
Categorical non-binary effect measure	1/34 (2.9)
Relative risk	1/1 (100)
Presentation of Results*	
Table	24/34 (70.6)
Text	32/34 (94.1)
Figure	21/34 (61.8
Posterior distribution	
Mean	1/34 (2.9)
Median	4/34 (11.8)
Not reported	29/34 (85.3)

*Studies were counted multiple times when more than one method was used.

Table 4. Aggregate journal characteristics

Characteristics	**Yes n/N (%) or Mean (SD)**
Impact factor	9.51 (8.75)
Supplement or appendix allowed	21/26 (80.8)
Online	19/21 (90.5)
Not specified	2/21 (9.5)
Word count limit	19/26 (73.1)
Table count limit	13/26 (50.0)
Figure count limit	13/26 (50.0)

Table 5. Individual journal characteristics

Journal	Included studies	Impact factor*	Supplement or appendix; format	Word count limit	Table limit	Figure limit
Alimentary Pharmacology & Therapeutics	Edwards, 2009a	3.861	Y, online	N	N	N
Annals of Internal Medicine	Gross, 2011	16.792	Y, not specified	3,500-4,000	4 tables or figures	4 tables or figures
Archives of Internal Medicine	Sciarretta, 2011; Cooper, 2006	10.639	Y, online	3,500	6 to 8 tables or figures	6 to 8 tables or figures
British Medical Journal	Baldwin, 2011; Hartling, 2011; Trelle, 2011; Wandel, 2010; Lam, 2007	13.471	Y, online	N	N	N
British Journal of Anaesthesia	Maund, 2011†	4.224	Y, online	5,000	N	N

Journal	Included studies	Impact factor*	Supplement or appendix; format	Word count limit	Table limit	Figure limit
British Journal of Cancer	Coon, 2009	4.831	Y, online	5,000-5,500	1 table reduces word limit by 200	1 figure reduces word limit by 200
British Journal of Ophthalmology	Van den Bruel, 2011	2.934	Y, online	3,000	5 tables or figures	5 tables or figures
Cancer Treatment Reviews	Golfinopoulus, 2009	6.811	N	N	N	N
Clinical Therapeutics	Edwards, 2009b	2.551	Y, online	5,500-6,000	N	N
Cochrane Database of Systematic Reviews	Walsh, 2010	6.186	N	N	N	N
Current Medical Research and Opinion	van de Kerkhof, 2011; Orme, 2010; Uthman, 2010; Vissers, 2010	2.609*	Y, online	11,200	N	N

Journal	Included studies	Impact factor*	Supplement or appendix; format	Word count limit	Table limit	Figure limit
Dermatology	Bansback, 2009	2.714	Y, not specified	13 pages for text, tables, figures	Included in page count	Included in page count
Drug and Alcohol Dependence	Meader, 2009	3.365	Y, online	6,000	N	N
Gastroenterology	Woo, 2010	12.023	Y, online	6,000	Minimum of 4 to 6 figures or illustrations	Minimum of 4 to 6 figures or illustrations
Health technology assessment (Winchester, England)	Maund, 2011†	4.197	N	N	N	N
The Journal of the American Medical Association	Phung, 2010	30	Y, online	3,500	4 tables or figures	4 tables or figures

Journal	Included studies	Impact factor*	Supplement or appendix; format	Word count limit	Table limit	Figure limit
Journal of Hospital Infection	Wang, 2010	3.078	N	5,000	N	N
Journal of Hypertension	Coleman, 2008	3.98	Y, online	N	N	N
Journal of the National Cancer Institute	Mauri, 2008; Kyrgiou, 2006	14.697	Y, online	6,000	8 table or figures	8 tables or figures
Lancet	Cipriani, 2009l Stettler, 2007	33.633	Y, online	4,500	"Should include about 5 illustrations"	"Should include about 5 illustrations"
Lancet Infectious Disease	Manzoli, 2009	16.144	Y, online	3,000-5,000	"Should include about 5 illustrations"	"Should include about 5 illustrations"
Lancet Neurology	Bangalore, 2011	21.659	Y, online	3,000-4,500	"Should include about 5 illustrations"	"Should include about 5 illustrations"

Journal	Included studies	Impact factor*	Supplement or appendix; format	Word count limit	Table limit	Figure limit
Lancet Oncology	Golfinopoulos, 2007	17.764	Y, online	3,000-5,000	"Should include about 5-6 illustrations"	"Should include about 5-6 illustrations"
Pharmacotherapy	Baker, 2009	2.631	N	7,000	N	N
Rheumatology	Nixon, 2007	4.171	Y, online	3,500	6 figures or tables	6 figures or tables
Value in Health	Dakin, 2010	2.342	Y, online	N	N	N

Abbreviations: Y: yes; N: no

*: The impact factor was obtained from Web of Science in 2012, except when the symbol appears for that journal the impact factor was not available in Web of Science and was taken from the journal's website.

†: Published as a manuscript and health technology assessment report, but counted as one unique publication

Appendix 1. Literature search

1. Randomized Controlled Trial/
2. Clinical Trial/
3. randomi$ control$ trial$.tw.
4. controlled clinical trial.sh.
5. clinical trial$.tw.
6. trial$.tw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. review literature/
9. meta-analysis.sh.
10. meta-analy$.tw.
11. metaanaly$.tw.
12. (meta adj analy$).tw.
13. 8 or 9 or 10 or 11 or 12
14. (indirect adj2 comparison$).tw.
15. (indirect adj2 evaluat$).tw.
16. (indirectly adj2 compare$).tw.
17. bayesian.tw.
18. (mixed treatment adj compar$).tw.
19. MTC.tw.
20. 14 or 15 or 16 or 17 or 18 or 19
21. 7 and 13
22. 20 and 21
23. limit 22 to english language
24. limit 23 to yr="2006 -Current"
25. remove duplicates from 24

Appendix 2. Network patterns

Examples of Networks with at least One Closed Loop

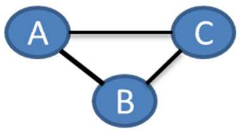


Figure 1

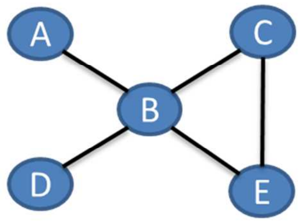


Figure 2

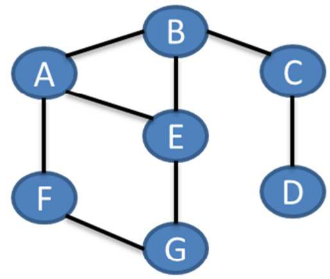


Figure 3

Examples of Networks without at least One Closed Loop

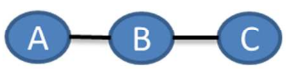


Figure 4

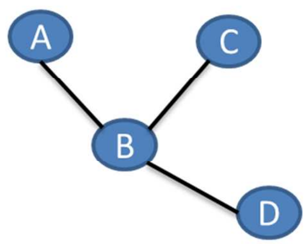


Figure 5

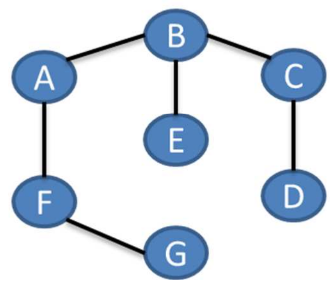


Figure 6

Here we provide examples of networks with (Figures 1-3) and without (Figures 4-6) at least one closed loop. A closed loop is defined as a comparison with a direct and indirect connection of evidence within the network. For example, in Figure 2, intervention B is compared to intervention C directly, but also indirectly through intervention E, making a closed loop. Presence of at least one closed loop defines the network as a mixed-treatment comparison.